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THE MANAGEMENT OF BLEEDING PEPTIC ULCER

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The management of bleeding peptic ulcer has been one of the greatest challenges to the surgeon over the past 35 years, as is attested to by the voluminous literature which has continued to appear year after year on this subject. The first successful surgical attack on a bleeding peptic ulcer was made in 1887 by Miculitz.[17] The modern method of surgical treatment of this disease was outlined by Finsterer[9, 10] of Vienna and by Allen[1, 2, 3] of Boston. Allen's work and criteria have remained valid and are perhaps the soundest foundation for the modern philosophy of the management of bleeding peptic ulcer. There are today few physicians who adhere to Meulengracht's[14, 15] precept that all patients suffering with this disease can be treated without surgical intervention. There is, however, considerable difference of opinion concerning the selection of patients for and the timing of the surgical procedure.[4, 8, 12, 13, 16, 18, 21] Moreover, once the surgical method of treatment has been elected, the surgeon is confronted by the problem of choosing one of a multiplicity of operative technics.[4, 7, 12, 21] For these reasons we feel justified in reporting our experiences in the management of bleeding peptic ulcer at the Veterans Hospital in Atlanta, Georgia, over a period of 9 years (1946 to 1955).

During this period there were admitted to this hospital 1,998 patients who had duodenal ulcer, 519 (26.0 per cent) of whom had evidence of gross bleeding,

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i.e., demonstrable hematemesis or melena within 48 hours before admission. The degree of bleeding varied from minor bleeding lasting only a day or so with no change in the hematologic picture to sudden, massive, exsanguinating hemorrhage leading to coma and death despite multiple transfusions of blood. These patients suffering with duodenal ulcer were under the care of a medicosurgical team consisting of the house staff, under the supervision of the faculty of Emory University School of Medicine, and the chiefs of sections at the Veterans Administration Hospital. With few exceptions, the surgical procedures were performed by the senior resident. The basic philosophy of treatment was that of practicing the art, as well as the science, of medicine. Each patient was considered individually. Patients were not grouped according to age, blood counts at the time of admission to the hospital, history of previous bleeding, duration of bleeding, et cetera, although it would not be fair to state that these factors had no influence on our decisions.

The patients were admitted to the hospital on the medical service and complete blood counts, determinations of hematocrit and other indicated hematologic studies, such as determinations of prothrombin time, bleeding and clotting times and nonprotein nitrogen levels, were done. Then the surgical and medical residents held a bedside conference and projected a plan of treatment. Usually

TABLE 1

Data on 519 cases of bleeding peptic ulcer

Group	Number of Cases		Age		Bleeding		Treated Surgically		Number of Deaths
			+45	−45	First	Recurrent	No.	Procedure	
I No hematologic change	132		23	109	96	36	0		0
II Diminished blood volume	314	221*	45	176	150	71†	0‡		0
Surgery elective		93§	32	61	14‖	79	46	High subtotal gastrectomy	1
							9	Gastroenterostomy with vagotomy	
							38	Hemigastrectomy with vagotomy	
III Surgery mandatory	73	64	29	35	30	34	26	High subtotal gastrectomy	8
							36	Hemigastrectomy with vagotomy	
							2	Plication of bleeding artery	
		9	8	1	6	3	0		9

* Included 6 cases of gastric ulcer.

† Included 18 of the 45 patients over age 45.

‡ Surgery was refused by patient in 12 cases and precluded by complications in 6.

§ Included 5 cases of gastric ulcer.

‖ Although these patients had not bled previously, other factors justified surgery.

it was evident at the first examination whether or not the patient was a candidate for immediate surgical intervention. If a period of observation seemed desirable, blood counts were repeated every 4 hours and sedative medication and small amounts of cream and antacid preparations were administered to the patient as indicated. Transfusions of blood were given whenever needed. If possible, a diagnosis was made before surgical treatment was undertaken.[6] In cases in which the patients were acutely ill we did not hesitate to perform roentgenographic examinations of their upper gastrointestinal tracts without palpation.[11, 19] Fortunately, in many cases ulcers had been demonstrated roentgenographically during previous hospitalizations.

Although, as pointed out above, the patients were not grouped at the time of treatment, it will be helpful for the purpose of analysis and discussion of the results of their management to divide them into three groups (table 1).

Group I comprised those patients who had no hematologic changes on admission, were not acutely ill and did not require surgical treatment. There were 132 patients in this group.

The patients in group II had had sufficient hemorrhage to cause some hematologic changes to be present at the time of their admission to the hospital. The duration of bleeding varied considerably in these patients. In every case the erythrocyte count was less than 3,800,000 per cubic millimeter, the pulse rate was elevated, and the patient showed clinically the loss of blood. Of the 314 patients in group II, 221 did not undergo surgery. Twelve patients refused to do so, 6 had complications which precluded any elective surgical procedure and in the remaining patients surgery was deferred for various reasons. Analysis does not differentiate in any way the patients who received no surgical treatment from the 93 patients who underwent elective surgical procedures when their clinical conditions and hematologic pictures became stabilized. Some of the latter patients were subjected to surgery because they had bled repeatedly, some because they had hemorrhaged rapidly or profusely and others because they gave histories of previously having had perforation, pain or other complications. All patients in this group ceased bleeding promptly on a medical regimen. Surgical treatment was elective. A high subtotal gastrectomy was performed in 46 patients, a gastroenterostomy with vagotomy in 9 and a hemigastrectomy with vagotomy in 38. Death occurred in 1 patient and was caused by homologous serum jaundice 6 weeks postoperatively. Early and late postoperative complications which occurred are listed in table 2.

In group III are the patients who were most affected by the controversial problems presently under discussion. In all of the 73 patients in this group it was thought that immediate surgical intervention offered the only hope of preventing death. Seventeen deaths (mortality rate, 23.3 per cent) occurred. None of the 9 patients who did not undergo surgery survived. In addition, 8 (12.5 per cent) of the 64 patients who underwent surgery died. A high subtotal gastrectomy was performed on 26 patients, a hemigastrectomy with vagotomy on 36, and plication of the bleeding artery on 2. There were postoperative compli-

TABLE 2

Postoperative Complications

Complication	Number of Cases in Which It Occurred		Number of Resultant Deaths
	Elective Surgery	Mandatory Surgery	
New bleeding ulcer	1		
Urinary shutdown		1	1
Pulmonary edema		1	1
Myocardial infarct	1	1	1
Cardiac arrest		1	1
Dehiscence	3	8	
Atelectasis	4	2	
Transfusion reaction	1		
Common duct cut	1		
Bleeding from suture line		1	
Dumping syndrome	5	2	
Bleeding from unremoved ulcer		3	1
Cerebrovascular accident		1	1
Wound infection; hematoma	3	1	
Mesenteric thrombosis		1	1
Hematuria	1		
Incisional hernia		3	
Diarrhea		1	
Acute cholecystitis and pancreatitis		1	
Duodenal stump blowout		2	1
Hepatitis	1	2	1

cations in approximately 60 per cent of these patients (table 2), which attests to the critical condition of the patients.

At this point attention should be called to the considerable variation in results of treatment of bleeding peptic ulcer reported by various authors. For example, Bowers and Rossett[5] reported a mortality rate of 1.3 per cent following treatment by a combined medicosurgical team in 150 cases of bleeding peptic ulcer, whereas Stewart and his colleagues[20] reported a mortality rate of 10.9 per cent following treatment with immediate replacement of blood and early subtotal gastrectomy in 110 cases. Since the high quality of work of both of these groups is well known, it must be assumed that the difference in results was due to a difference in the type of patients in the two series. It is for this reason that we believe it may be enlightening to present here an individual report of each of the 17 patients who had bleeding peptic ulcer in our series in whom death occurred, either postoperatively or when no surgical procedure had been performed. We believe that the high percentage of patients in whom treatment was successful justifies the method of management. Three of the 9 patients in group III who did not undergo surgery and who died were treated during the first 3 years of our study. It is thought that patients presenting similar problems now would be treated surgically.

REPORTS OF CASES

Case 1. A 66 year old man with a 12 hour history of severe bleeding was admitted to the hospital, at which time his hemoglobin was found to be 9.8 Gm. per 100 cc. of blood. Transfusions of a total of 7,500 cc. of blood were given during the first 24 hours following his admission. A subtotal gastrectomy was performed on the third day of his hospitalization. Death occurred on the seventh postoperative day due to generalized peritonitis following a "blowout" of the duodenal stump.

Comment. If surgery had been undertaken earlier, before depletion of tissue protein, this patient would have had a better chance to recover. Prompt drainage of the duodenal stump also might have altered the outcome.

Case 2. This 27 year old white male was admitted to the hospital 12 hours following the onset of severe hemorrhage. During the next 72 hours he received by transfusion 11,500 cc. of whole blood, following which he underwent surgery. On the first postoperative day atelectasis and dehiscence were noted. Death, due to cardiac arrest, occurred during a bronchoscopic examination.

Comment. A surgical procedure was performed on a protein-depleted, physiologically exhausted patient. Earlier surgery was indicated.

Case 3. This 49 year old white man was hemorrhaging severely and was in a state of shock at the time of his admission to the hospital. He responded well to treatment with replacement of blood but continued to bleed. A subtotal gastrectomy was performed, but the ulcer was not removed. On the first postoperative day the patient again went into a state of shock and death resulted from continued bleeding from the unremoved ulcer.

Comment. The ulcer should have been removed or at least exteriorized from the gastrointestinal field.

Case 4. This 23 year old white man had severe hematemesis and melena for 5 days prior to entering the hospital. He had received several transfusions of blood elsewhere. At the time of his admission he was in a state of shock. His erythrocyte count was 2,600,000 per cubic millimeter. During the next 13 hours 7,000 cc. of whole blood and 2,000 cc. of glucose in normal saline were administered. At the time of surgery it was discovered, during the process of removing the lower half of the stomach, that the bleeding point was in the fundus and this was controlled by ligation. The patient did well immediately following the surgical procedure. Death, due to pulmonary edema (confirmed by autopsy), was precipitated by the administration of an additional 1,000 cc. of whole blood.

Comment. 1. This patient underwent an unnecessary subtotal gastrectomy. The bleeding point in the fundus might have been detected preoperatively by roentgenography and would certainly have been detected by a preliminary gastrotomy and duodenotomy with exploration. 2. Analysis revealed that a total of 10,750 cc. of fluid had been administered to this patient intravenously over a period of 13 hours. That this intake exceeded his capacity was demonstrated by his death. The 2,500 cc. of normal saline which was administered could have been omitted. Probably most or all of the fluid that this patient received should have consisted of blood, without the additional electrolytes. He should not have been given the last transfusion of 1,000 cc. of blood. 3. Digitalization of the patient might have been of some value.

Case 5. This 58 year old white man had severe hypertension and had had acute cardiac failure off and on during the previous 4 years with grade 4+ cardiomegaly. He was syphilitic and an alcoholic addict. Six months before entering the hospital he had had a gastroenterostomy with vagotomy for pyloric obstruction. Twenty-four hours prior to his admission he had begun to have melena. At the time he was admitted his hemoglobin was found to be 6.4 gm. per 100 cc. of blood and his hematocrit, 23 per cent. Roentgenograms revealed a marginal ulcer and a duodenal ulcer, one of which was thought to be the source of the bleeding. A subtotal gastrectomy was performed approximately 8 hours after the patient entered the hospital. He continued to bleed postoperatively and died 33 days later, having received a total of 22,000 cc. of blood by transfusion. Autopsy revealed the source of the bleeding to be an unrecognized gastric ulcer.

Comment. This case corroborates our belief that an attempt should be made to detect the bleeding point at the time of surgery, even though a roentgenographic diagnosis has been made preoperatively.

Case 6. This 38 year old Negro male had malignant hypertension (blood pressure, 260 mm. of mercury systolic and 150 mm. diastolic) with grade 3+ albuminuria with many red blood cells and casts in the urine, and grade 3 changes in his eye grounds. He had been having severe melena and hematemesis for 24 hours prior to entering the hospital. Determination of his hemoglobin revealed 6 gm. per 100 cc. of blood. Shortly after his admission an ulcer crater was demonstrated roentgenographically. The administration of 9,000 cc. of blood during the next 48 hours effected no diminution of the bleeding and little improvement in the blood counts. After hesitating approximately 48 hours on account of the patient's concomitant malignant hypertension, it was decided to undertake surgical intervention and a subtotal gastrectomy was performed. The patient responded well until the fifth postoperative day, when he developed urinary "shutdown" and shortly thereafter died.

Comment. A calculated risk was run and lost in this case.

Case 7. This 38 year old white man gave a history of having had an ulcer, which had been confirmed roentgenographically, for 10 years. At the time of his admission to the hospital he had been bleeding for 3 days. His erythrocyte count was 2,100,000 per cubic millimeter. Transfusions of 8,000 cc. of blood were administered within the first 48 hours, following which a subtotal gastrectomy was performed. Although his postoperative course was uneventful for 6 days, he then developed a mesenteric thrombosis and subsequently was found to have large bilateral subphrenic abscesses, which were drained. He passed several loops of gangrenous small intestine from these abscesses. Biliary fistulas developed and three episodes of severe jaundice occurred. Two attempts were made surgically to re-establish continuity of the small intestine. However, a multiplicity of other complications developed and 4 months postoperatively the patient died.

Comment. This patient's postoperative complications and death probably were not related to the bleeding duodenal ulcer.

Case 8. This 52 year old man had bled slowly but steadily for 2 weeks before entering the hospital. Two years previously he had had a cerebrovascular accident. During the 60 hours following his admission he was given 6,000 cc. of blood at an even rate, which raised his erythrocyte count from 2,100,000 per cubic millimeter to 3,800,000. A subtotal gastrectomy was performed, at which time 2,000 cc. of blood were administered. Thirty minutes following the surgical procedure the patient died, his death apparently being caused by a second cerebrovascular accident.

Comment. It was decided, with some trepidation, to undertake surgical treatment of the bleeding peptic ulcer in this case despite an increased risk due to the concomitant disease. In retrospect, however, we are still of the opinion that the decision was justified.

Case 9. This 21 year old white man at the time of his admission to the hospital was in a state of shock, having hemorrhaged severely for 4 days previously. His erythrocyte count was 1,800,000 per cubic millimeter. Within the next 32 hours the patient received 7,000 cc. of blood and 4,000 cc. of electrolytes. He died, never having recovered from his vascular collapse. Necropsy revealed pulmonary edema and bilateral pleural effusion.

Comment. This patient had received inadequate replacement of blood during the 4 days prior to his admission. On the other hand, following his admission, he probably was given excessive fluid in the form of electrolytes, which may have helped to precipitate the pulmonary edema. Moreover, we now are of the opinion that the bleeding point should have been controlled by surgical means with the aid of arterial transfusions.

Case 10. This 50 year old white man was admitted to the hospital in a state of shock 4 days following the onset of severe melena and hematemesis. His erythrocyte count was 1,900,000 per cubic millimeter. During the next 62 hours 24,500 cc. of whole blood were administered without any response, and the patient died. Autopsy revealed moderate pulmonary edema and erosion of the pancreaticoduodenal artery through the floor of the ulcer.

Comment. Again in this case irreversible shock was present which failed to respond to massive replacement of fluid, perhaps because the ulcer continued to bleed. In retrospect, it is our opinion that a surgical attempt should have been made to stop the bleeding, with the aid of arterial transfusions.

Case 11. This 53 year old white man had malignant hypertension (blood pressure, 250 mm. of mercury systolic and 140 mm. diastolic). At the time he entered the hospital he had been bleeding fairly slowly for 16 hours and his erythrocyte count was 2,300,000 per cubic millimeter. Shortly after his admission a gastric ulcer in the midportion of the posterior wall of the stomach was demonstrated roentgenographically. The patient received 7,500 cc. of blood during the next 11 days, but his hemoglobin did not rise. On the eleventh day rapid massive hemorrhage and death occurred.

Comment. Surgical treatment of the bleeding ulcer was considered contraindicated in this case because of the increased risk due to the patient's hypertension. In retrospect, however, despite postoperative death in a similar case reported above (case 6), we now are of the opinion that in this case the chance of successful surgery and recovery outweighed the increased risk and therefore should have been attempted.

Case 12. This 65 year old white man was admitted to the hospital because of severe pulmonary emphysema. While in the hospital, he perforated a duodenal ulcer, which was repaired under local anesthesia. Following this, he developed bilateral pneumothorax, which was treated with thoracotomy tubes. While in an oxygen tent on the eighth postoperative day, he began to have tarry feces. Two days later he entered a state of shock and died.

Comment. At no time was surgical treatment for bleeding peptic ulcer considered in this case on account of the delicate condition of the patient.

Case 13. This 51 year old man was admitted to the hospital suffering with marked pulmonary emphysema. He gave a history of recent weight loss and constant, chronic gastrointestinal bleeding. Shortly after being admitted he perforated a duodenal ulcer, which was closed under local anesthesia. On the fifth postoperative day the patient developed intestinal obstruction. Two days later he began to have melena. On the eleventh postoperative day massive hemorrhage occurred and, although he was given 2,500 cc. of blood, the patient died.

Comment. A second surgical procedure was not considered.

Case 14. This 74 year old man was admitted to the hospital in a state of mental confusion and disorientation. On the day of admission he had had severe, rapid hemorrhage, which continued for 48 hours. There was clinical evidence of cirrhosis and esophageal varices, and this was confirmed by laboratory tests and roentgenograms. Autopsy revealed in addition, a large gastric ulcer.

Comment. Although the varices probably were the source of the bleeding, this case is included in our series because of the presence of an ulcer.

Case 15. This 64 year old man was blind, deaf and quite obese and had uncompensated severe arteriosclerotic disease of the heart. At the time of his admission to the hospital he had been having severe hematemesis and melena of unknown duration. There was electrocardiographic evidence that he previously had had a coronary infarct. His hemoglobin was 6.7 gm. per 100 cc. of blood and hematocrit 24 per cent. Determinations of his carbon dioxide combining power revealed it to be above normal and his serum chloride was below normal. He continued to have melena and hematemesis and died on the eleventh day after admission. Autopsy revealed bilateral pleural effusion and ruptured duodenal and gastric ulcers.

Comment. Because of the patient's condition, it was thought that surgical intervention was contraindicated in this case.

Case 16. This 66 year old white man had marked left ventricular hypertrophy, bilateral thrombophlebitis in the lower extremities, right hemiplegia and aphasia, and severe nocturnal dyspnea. He had had several pulmonary infarcts and had been taking dicumarol. At the time of his admission to the hospital his hemoglobin was found to be 16.4 gm. per 100 cc. and his hematocrit 50 per cent. Roentgenograms made during a previous hospitalization had demonstrated a duodenal ulcer. Because of his polycythemia, he was given only 500 cc. of blood. He died on the fifth day after admission.

Comment. In view of this patient's condition, no serious consideration was given to surgical treatment.

Case 17. This 57 year old man was admitted to the hospital in July of 1952, at which time he had been having hematemesis and melena and was in a state of severe shock. His erythrocyte count was 1,500,000 per cubic millimeter. Multiple transfusions were given, but the patient died 7 days after his admission. During the first 4 days of hospitalization he had refused to undergo further surgery; during the last 3 days we declined to perform it.

This patient previously had undergone several operations. In 1944 at another hospital a gastroenterostomy had been performed for treatment of a duodenal ulcer. Subsequently he had developed a marginal ulcer and a vagotomy had been performed at the Veterans Administration Hospital, Atlanta, Georgia, in 1945. Later he had been admitted to this

hospital again suffering with a marginal ulcer. In 1951 he had been readmitted and found to be bleeding from his ulcer with obstruction, for which a laparotomy had been performed. The ulcer had continued to bleed, and later in the same month the patient had undergone a subtotal gastrectomy. Later during this same period of hospitalization he had had drainage of a subphrenic abscess and a hematoma, at which time the spleen had been torn. The following day a splenectomy had been done. He had recovered from these multiple procedures.

Comment. This patient had ulcer diathesis. His case represents a failure of medical and surgical treatment of ulcer. It was difficult to decide in which group this case should be classified in this discussion. Since the patient received no surgical treatment during his terminal illness, the case was assigned to the group in which no surgery was performed.

Miscellaneous case. Although this case is not included in our series, it is being reported in order to point out another pitfall in the management of bleeding peptic ulcer. The patient was a 57 year old alcoholic addict who gave a history of having an ulcer. At the time of admission to the hospital he had been having melena for 36 hours. His erythrocyte count was 2,900,000 per cubic millimeter. Roentgenography after ingestion of barium disclosed no esophageal varices and the duodenal cap appeared normal. The patient had no hemoptysis but continued to have melena and was in a state of shock most of the time despite massive replacement of blood. After having refused surgical intervention for a period of 5 days, he then consented to undergo it. At the time the surgical procedure was performed no blood was noted in the upper gastrointestinal tract and no ulcer was found. A "blind" gastrectomy was done. Months later a bleeding polyp of the sigmoid was demonstrated and removed surgically.

Comment. This case was very instructive. In retrospect, it seems obvious that the absence of (1) hematemesis, (2) any evidence of peptic ulcer on roentgenographic examination and (3) blood in the stomach and small intestine at the time of surgery indicated that the site of the pathologic process was elsewhere.

SUMMARY

The management of bleeding peptic ulcer has been discussed. The literature on this subject has been reviewed briefly. Problems to which special attention has been given include the selection of patients for and the timing of surgical intervention and also the choice of the operative technic.

We have outlined the methods of treatment of the 519 patients suffering with bleeding peptic ulcer who were admitted to the Veterans Hospital, Atlanta, Georgia, during a 9 year period (1946 to 1955), and have analyzed the results. Seventy-three of these patients were considered to be in need of immediate surgical treatment. Of this number, none of the 9 patients who did not undergo surgery survived and 8 (12.5 per cent) of the 64 patients on whom surgical procedures were performed died.

In order to reveal the types of patients included in this series and also to point out methods for attempting to decrease the mortality rate in patients who have bleeding peptic ulcers, an individual report, with comment, is presented of each of the 17 patients in this series in whom death occurred, either postoperatively or when no surgical procedure had been performed.

CONCLUSIONS

Massively bleeding peptic ulcer is most effectively managed by a medico-surgical team.

If surgical treatment is elected, it should be performed without delay.

Replacement of blood and fluid should be administered generously preoperatively, but rather conservatively postoperatively.

Conclusions concerning surgical technic: (a) If possible, the diagnosis should be confirmed preoperatively by roentgenographic examination; otherwise, by surgical exploration. (b) From our experience, we regard hemigastrectomy with vagotomy as the surgical procedure that offers the best immediate and long term results. (c) At the time of surgery the ulcer should be removed or exteriorized. (d) In certain cases "blind" gastrectomy may be indicated.

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PROCESSING OF ARTERIAL GRAFTS

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Of the various arterial prosthesis, the arterial homograft has proved to be the most satisfactory. There have been numerous ways used to process these homografts. The most satisfactory is the freeze-dry processing. Various apparatuses have been devised for this method, however, the most convenient is the glass manifold type. This is superior to the more complicated varieties in that it is relatively inexpensive and simple. An inexpensive system suitable for a small vascular service will be discussed.

Figure 1 shows the glass manifold system that we are currently using. This apparatus has 3 cold traps and 2 ports for processing vessels. The Stokes gauge is used to measure the vapor pressure within the system; a standard mega-vacuum pump is used to obtain negative pressure. The criteria that we use for donors (figure 2) are as follows: The donor must be less than 40, must die a traumatic death, or suddenly from intracranial hemorrhage, or other causes, with no evidence of septicemia or malignancy. The graft then is taken within 6 hours if the body is not refrigerated or within 18 hours if the body is refrigerated in the morgue.

After obtaining the graft, processing may be directed along two lines (figure 3) depending on whether the graft was taken under aseptic or unsterile technic. If taken under sterile conditions the graft is immediately placed in a chilled saline solution containing penicillin and streptomycin* and then carried to the laboratory. Here in the laboratory the graft is rapidly frozen at −70 degrees centigrade and then attached to the glass manifold. If the graft is taken unsterilely, sterilization is performed by immersing the graft in ethylene oxide for 30 minutes. Following this, the excess ethylene oxide is removed and the graft frozen at the same temperature of −70 degrees centigrade. The only difference in this method is that, during the processing, liquid nitrogen must be used in the traps, because ethylene oxide must be chilled below −180 degrees centigrade to condense. If liquid nitrogen is not used, the ethylene oxide will dilute the oil in the vacuum pump, rendering the vacuum ineffective.

According to the histologic work by G. H. Scott[1], it has been shown that at a temperature warmer than −33 degrees centigrade, ice crystals develop within the cell and actually rupture the cell membrane. At temperatures colder than this these ice crystals are exceedingly small and do not disfigure the normal architecture. Furthermore, it has been shown that blood vessels stored for pro-

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* This sterile saline solution contains 1,000,000 μ of aqueous penicillin and 1.0 gram of streptomycin for each 1000 cc. of saline.

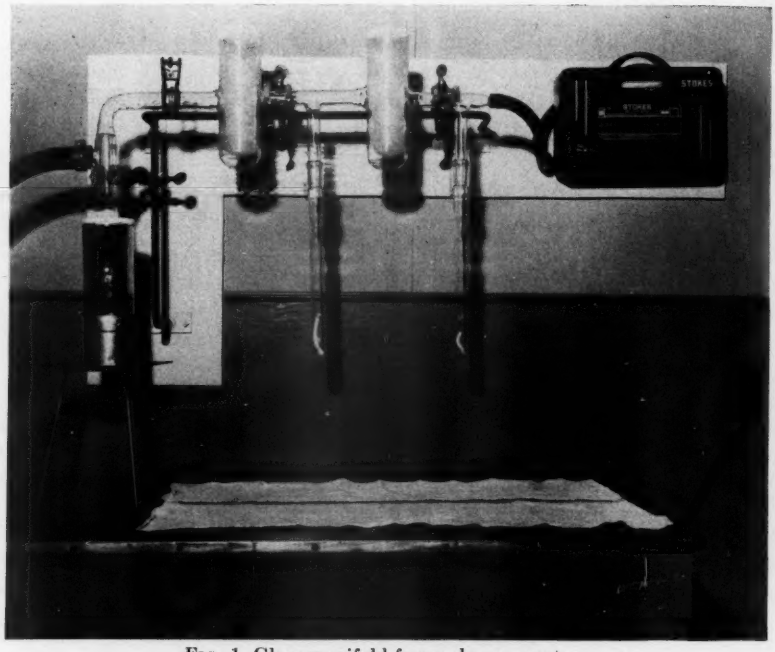

FIG. 1. Glass manifold freeze-dry apparatus

—CRITERIA—

1. Donor less than 40.
2. Traumatic death.
3. No infection or malignancy.
4. Graft taken within 6 hours if body is not refrigerated.
5. Graft taken within 18 hours if body is refrigerated.

FIG. 2. Criteria for donor of arterial graft

—PROCESSING—

Sterile

1. Graft placed in chilled sterile saline with penicillin and streptomycin.
2. Frozen at −70°C (CO_2-acetone).
3. CO_2-ether (−126°C) as trap coolant.

Unsterile

1. Graft placed in chilled saline.
2. Ethylene oxide, 30 minutes for sterilization.
3. Frozen at −70°C (CO_2-acetone).
4. Liquid nitrogen used as coolant (−190°C).

FIG. 3. Alternative methods of processing arterial grafts

—VAPOR PRESSURE OF H_2O—

760.000 mm Hg	100°C
4.58 mm Hg	0°C
0.286 mm Hg (286 μ)	−30°C
0.187 mm Hg (187 μ)	−34°C
0.096 mm Hg (96 μ)	−40°C
0.01 mm Hg (10 μ)	−48°C

FIG. 4 Vapor pressure of H_2O at various temperatures

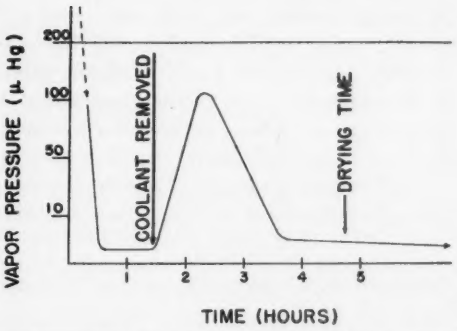

FIG. 5 Vapor pressures recorded during the drying of an arterial graft

longed periods in a frozen state at −27 degrees centigrade are inferior, when used as grafts, to those that have been stored at −70 degrees centigrade. Although no definite observations have been made as regards the critical drying temperature during the freeze-drying of arterial segments, one can say empirically that it is safe if the temperature of the specimen does not rise above −33 degrees centigrade until the specimen is nearly dry. During the actual processing of an arterial homograft the temperature of the vessel cannot be measured. However, the vapor pressure of the liquid in the glass manifold can be measured by use of various types of vacuum gauges.

From figure 4 we see that vapor pressure of water at 760 millimeters of mercury is equal to a 100 degrees centigrade temperature. A vacuum pressure of 187 microns is equal to a −34 degrees centigrade. At vacuum pressures less than 187 microns it is seen that the corresponding temperature is adequate to prevent arterial graft destruction. It is, therefore, imperative that during the entire drying process the vacuum pressure within the drying system must be maintained below 187 microns of mercury pressure. During the drying process, as soon as the vacuum pump has been started, it can be seen in figure 5 that the vacuum pressure rapidly falls, in this case it fell to 5 microns of mercury pressure. During the first hour and a half of drying the grafts are kept submerged in an alcohol-dry ice mixture with a temperature of −70 degrees centigrade. This is used to protect the graft until maximum vacuum has been obtained. After this vacuum has been obtained, the coolant is removed from around the homograft and drying takes place. It will be noted that upon removal of the coolant the vapor pressure rises. This is due to the rapid sublimation of the water within the graft. Should this pressure rise above the critical level of 187 microns then the coolant must be replaced around the graft to slow down sublimation. With completion of sublimation within the graft, the vacuum pressure will gradually return to the previous level. At this point it has been shown that the drying process is approximately 80 per cent completed, however, to obtain a moisture content of the homograft of less than 1 per cent the vacuum must be maintained for a period of 8 hours.

At the end of the drying process, the grafts are sealed under vacuum and stored at room temperature until they are used. At the time of surgery the sealed test tubes are sterilized by soaking in a liquid sterilizing solution and reconstituted by soaking for 30 minutes in body temperature saline. We have thought that grafts taken under sterile conditions are superior to those which have been sterilized with ethylene oxide. In those grafts sterilized with ethylene oxide the vessel walls seem to be softer and less elastic. There have also been several cases of aneurysmal formation in grafts used that have been sterilized in this manner.

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DUODENAL DIVERTICULA WITH SPECIAL REFERENCE TO THE FIRST PORTION OF THE DUODENUM

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INTRODUCTION

Chomel[12] in 1710 was the first to describe diverticulum of the duodenum. Case[9, 10] was the first to demonstrate duodenal diverticula by means of x-ray. Key is credited with the first operation in 1915[36]. Morton[28], Patterson and Bromberg[32], Cattell and Mudge[11], and Waugh and Johnston[36] have presented summaries of the cases of patients who were treated surgically through 1952.

Although reports of duodenal diverticula are not uncommon, the total number treated surgically, as reported in the literature, is relatively small. This may be a reflection of the fact that many of these are asymptomatic. This may also reflect the fact that there is some difficulty in deciding whether the diverticulum which happens to be present is the basis for the patient's symptomatology.

Incidence: The incidence of duodenal diverticula, as reported in the literature, varies with two important factors. One of these is the type of clinic or hospital reporting the series. The other is whether the series is based on anatomic dissections (careful autopsies) or x-ray examinations. From table 1 it is obvious that there is a difference in the occurrence of duodenal diverticula as discovered by x-ray examinations (gastrointestinal series). This varies from the figure of 0.8 per cent as reported by Glasier and Corbett[18] to the figure of 5.76 per cent as reported by Chitambar[12]. The figures for the incidence of duodenal diverticula based on autopsy studies varies from the 5 per cent of Horton and Mueller[21] to the 22 per cent of Ackermann[1].

It is important to remember that the x-ray studies are based on those patients who have symptomatology referable to the gastrointestinal tract, thus presenting an indication for the gastrointestinal series.

The figures quoted above are for the total occurrence of duodenal diverticula, whether single or multiple. Multiplicity is not uncommon in duodenal diverticula. Multiplicity is found to occur in from 11 to 26.7 per cent of the cases[11, 28, 34, 36, 37]. Sometimes the diverticulum is a rounded, globular affair, sometimes it is bilobed, and sometimes it may present small mushroom-like, daughter diverticula arising from the circumference of the original diverticulum.

Age: Duodenal diverticula have been found in patients of all ages. However, it is uncommon to find them in persons under the age of 30 years. The majority are seen in the fifth or sixth decades of life. Table 2 lists the average age as reported in several series in the literature. The range is from 53.3 years to 63.7 years. The average for this group is 58.04 years. It is important to remember that the age as reported is colored by the fact that many of these series are based

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TABLE I

Incidence According to Discovery by X-ray and Autopsy Studies

X-ray	Per Cent	Autopsy	Per Cent
Browne and McHardy[8]	5.3	Ackermann[1]	22
Chitambar[12]	5.76	Baldwin[2]	14.5
Weintraub and Tuggel[38]	2.4	Grant[19]	11.6
Cattell and Mudge[11]	1.9	Horton and Mueller[21]	5
Glasier and Corbett[18]	0.8	Nagel[29]	2.2

TABLE 2

Average Age

	Age
Case[9]	56
Beales[3]	53.3
Edwards[13, 14, 15]	53.8
Finney[16]	63.7
Warren and Emery[35]	58.07
Chitambar[12]	63.37
Average	58.04

on the time of occurrence of symptomatology. It is quite possible that these diverticula might have been present many years prior to the development of symptoms which called attention to the anatomic abnormalities.

Sex: Although there is a slight difference of opinion among the various authors there does not seem to be any definite sex predominance. Some authors report a slight preponderance of women in their series, others report a slight preponderance of males, and still others are about equally divided.

Location: A review of the literature reveals fairly widespread agreement that the second portion of the duodenum is the portion which most frequently contains diverticula. From a series of 13 reviews[1, 2, 3, 8, 9, 10, 11, 12, 13, 14, 15, 16, 32, 35, 36, 37, 38] a total of 785 instances of duodenal diverticula are reported, with 66.6 per cent occurring in the second portion, 28.7 per cent in the third portion, and 4.7 per cent in the first portion.

It is usually written that the diverticula arising in the second portion of the duodenum take their origin from the concave or inner border, in close proximity to the head of the pancreas and the common bile duct. It also has been stated that diverticula are almost always found on the side of the blood supply of the duodenum[25]. However, Chitambar[12] has shown that this is not true and that in the first portion of the duodenum, diverticula were found on both the superior and inferior aspects, and in the second portion were found on the medial and lateral aspect, and in the third portion were found on the superior and inferior aspects.

The diverticula of the duodenum are more commonly located posteriorly than

anteriorly[11]. Usually it is necessary to mobilize and reflect the second portion of the duodenum in order to dissect out the neck of the diverticulum. Cattell and Mudge[11] found the diverticulum presenting on the posterior aspect of the duodenum in 60 per cent of their cases, and on the anterior aspect in 20 per cent of their cases of duodenal diverticula of the second portion of the duodenum.

Classifications: Numerous methods of classifying duodenal diverticula have been used. These include true and false, pseudo- and genuine, acquired and developmental. The classification based upon the etiology of the duodenal diverticulum is a simple one which avoids a great deal of the confusion attached to the other methods of classification. Primary duodenal diverticula are thin outpouchings of the wall in communication with the bowel and not the result of any apparent intrinsic or extrinsic disease. Secondary duodenal diverticula are due to traction or scarring from inflammatory processes extrinsic to the bowel. These inflammatory processes produce adhesions and traction as a result of the local scarring. According to some authors in most cases the primary duodenal diverticula contain no muscle layers in the walls. This has been found to be true except at the neck of the duodenal diverticulum. It is at this point that one may see muscle in the wall of the neck of the duodenal diverticulum but as one traces the wall outward away from the lumen of the intestine the muscle layers disappear. Occasionally muscle may be seen in the entire diverticulum wall. Usually in the secondary type of duodenal diverticulum the normal layers are seen in the wall, corresponding to those of the duodenum itself.

Etiology: The conditions necessary for the development of a diverticulum are considered to be: 1) the lack of intrinsic muscle tone; 2) loss of support of connective tissue around the blood vessels; 3) changes incidental to the age; and 4) pulsion and intraluminal pressure increase.[5, 13, 14, 15, 16, 30]

Most diverticula occur on the concave border of the duodenum and on the mesenteric border. This is the site of entrance of blood vessels, bile ducts, and pancreatic structures. This point of entrance is considered to be a weak spot in the muscular coat. It also is a spot where fat is seen entering the wall of the duodenum and reaching the submucosa. The fat may produce a weakness or defect in the muscle layer[7]. Boyd believes that this weakness is combined with intraluminal pulsion, forming a dilatation which is similar in nature to an aneurysm[7]. The wall of the duodenal diverticulum is most often composed of only mucosa and muscularis mucosae, these being protruded through the muscular layer.

Diverticula of the first portion of the duodenum are definitely less common than those of the second and third. A first portion diverticulum, when not secondary to ulcerations, probably is a true, congenital diverticulum. However, ulceration with increased intraluminal pressure may cause a diverticulum formation. Boyd[7] described this process in the first portion of the duodenum. Edwards[13, 14, 15], Beales[3] and Freelander[17] believe that all diverticula of the first portion of the duodenum are associated with the presence of peptic ulceration. Chitambar[12] found that in his series all those with diverticula of the first portion

of the duodenum had had a perforation of a duodenal ulcer previously. The case reported in this article revealed no evidence of a duodenal ulcer.

Duodenal diverticula may be associated with the presence of diverticula elsewhere in the gastrointestinal tract. According to Chitambar[12] 31 per cent of his patients had diverticula in other portions of the gastrointestinal tract. He also found that 13.3 per cent had diverticula in portions of the small intestine other than the duodenum.

The descriptive characteristics of duodenal diverticula vary. The size may vary from a few mm. to several cm. in diameter. The shape may be globular, funnel shaped, or cylindrical. Bilobed and other bizarre shapes have been noted in duodenal diverticula cases. Chitambar[12] described such shapes as mushroom shaped, bilobed, lobulated, and daughter implantation type of diverticula. The author's case contained a large mushroom shaped, lobulated diverticulum with what could be described as daughter diverticula (fig. 6).

Pathology: Two-thirds to three-fourths of all primary duodenal diverticula originate from the medial concave border of the second portion of the duodenum. Next in frequency in the site of origin is the superior margin of the third portion of the duodenum. Primary diverticula rarely occur in the first portion of the duodenum. When they are in this location they are said to arise as a rule from the superior border[20]. Duodenal diverticula may be multiple in about 10 per cent of the cases.[20]

When the diverticulum arises from the concave border of the duodenum, it usually protrudes into the pancreatic tissue. That is, the presentation is medial. Occasionally the presentation is posterior. Anterior presentation is unusual. In the transverse portion of the duodenum the presentation is cephalad and the diverticulum usually is covered by the transverse mesocolon.

The wall of the duodenal diverticulum may exhibit the same type of inflammatory reactions as normal duodenal lining will show. Gangrene and perforation have been recorded (gastric mucosa has been reported in the wall of the diverticulum)[11]. Ulceration has been reported within the duodenal diverticulum. Bleeding is not uncommon[36]. Pancreatic tissue and biliary calculi have also been reported to be found in a duodenal diverticulum[11]. Recurrence of a neoplasm in a duodenal diverticulum has been described[27]. Perforation of a duodenal diverticulum may occur [18]. Acute and chronic pancreatitis have been found in association with the occurrence of a duodenal diverticulum presenting in the pancreas[18].

Symptomatology: The incidence of positive symptoms in proved duodenal diverticula varies from 8 per cent[4] to 75 per cent[26]. Whipple[39] gives an incidence of symptoms of 50 per cent. The diagnosis of symptoms due to the presence of a duodenal diverticulum is largely one of exclusion of other disease processes which might conceivably cause such symptoms and the presence of a duodenal diverticulum. (See Tables 3 & 4).

There is no characteristic symptom complex associated with a duodenal diverticulum. If the duodenal diverticulum is the seat of a pathologic process, these symptoms may be those of the associated process and its complications.

Diagnosis: Although the preoperative diagnosis is made only by means of an upper gastrointestinal series, a duodenal diverticulum may easily be missed

TABLE 3

Symptom Production[11, 12, 18, 28, 36, 37]

A. Mechanical Causes Producing
   1. Delayed emptying of diverticulum.
   2. Pressure on common duct.
   3. Pressure on pancreatic duct.
   4. Obstruction of the duodenum.

B. Inflammatory Causes Producing
   1. Ulcer syndrome.
   2. Gall bladder syndrome.
   3. Pancreatitis syndrome.
   4. Pylorospasm syndrome.
   5. Hemorrhage.
   6. Perforation.

C. Neoplasia.

TABLE 4

Symptoms[11, 12, 13, 14, 15, 18, 20, 36, 37]

1. Pain
   a. Right upper quadrant, epigastric, periumbilical, upper abdominal, interscapular, costovertebral angle.
   b. Made worse or brought on by a large meal.
2. Constipation.
3. Belching.
4. Nausea.
5. Vomiting.
6. Weight Loss.
7. Jaundice.
8. Diarrhea.
9. Long history with periods of remission.

TABLE 5

Complications[6, 11, 12, 18, 20, 22, 31, 36, 37]

1. Acute Inflammation.
2. Ulceration.
3. Perforation.
4. Hemorrhage.
5. Neoplastic Change
6. Calculi (primary or secondary from biliary tree).
7. Obstruction.
   a. Pancreatic.
   b. Duodenal.
   c. Biliary.
8. Peridiverticulitis with Adhesion Formation.
9. Fistula Formation (usually cholecystoduodenal).
10. Duodenitis.
11. Cholangitis.
12. Acute Pancreatitis.
13. Chronic Pancreatitis.

during this examination. The gastrointestinal series is the only definite method of making the diagnosis because of the lack of a definite characteristic history for this lesion. In addition most duodenal diverticula are asymptomatic. Therefore one must rule out all other diagnostic possibilities. Even after other pathologic processes have been ruled out, disagreement may still remain as to the possibility that the symptomatology is due to a duodenal diverticulum.

Complications: Table 5 lists the various complications which have been reported secondary to duodenal diverticula.

Treatment: If it is thought that the symptomatology present is due to a duodenal diverticulum, conservative medical management should be tried. This consists of correcting dietary indiscretions, following a bland, postulcer type of diet; rest; proper regulation of bowel movements; and postural drainage.

If the duodenal diverticulum is discovered accidentally, and is asymptomatic, then no definite treatment should be carried out. It is estimated that approximately 5 per cent of duodenal diverticula will be the basis for symptomatology and will require surgery[33]. This is actually 5 per cent of those people with a duodenal diverticulum.

Surgery is indicated when any of the complications of duodenal diverticula have occurred. Surgery also is indicated in those patients with definite symptoms which have been shown to be due to the duodenal diverticulum.

Whenever operation is undertaken for a duodenal diverticulum, the surgeon must do a complete exploratory laparotomy before attacking the diverticulum. There are several methods open for attacking the diverticulum. The best of these is total excision of the lesion. If for some reason the duodenal diverticulum is inverted one must be very careful because obstruction may be produced.

Duodenal diverticula in the first part of the duodenum presents less difficulty in exposure and approach than in the other portions of the duodenum. Subtotal gastrectomy has been performed for excision of a diverticulum of the first portion of the duodenum. However, this seems somewhat radical unless there is associated ulceration. It is possible to excise the duodenal diverticulum in the first portion of the duodenum by reflecting the entire duodenum medially and excising the sac flush with the duodenal wall.

The duodenal diverticulum in the second portion of the duodenum presents a little more difficulty. The dangers of damage to the pancreas with leakage and of bleeding during the dissection are great. Identification of the duodenal diverticulum in the second portion of the duodenum presents some difficulty also. Among the maneuvers described to aid in the identification of the duodenal diverticulum of the second portion are: distention of the diverticulum with gas[16, 25]; inserting finger into the duodenal diverticulum through a duodenotomy opening[23, 24] and a choledochotomy with the insertion of a probe in the common duct[36, 37].

Diverticula of the third portion of the duodenum present a very difficult problem. The approach is relatively inaccessible and is through the transverse mesocolon. If necessary, the ligament of Treitz may be divided.

In attacking a diverticulum surgically, simple inversion of a very small

diverticulum has been carried out. However, this presents a potential danger of partially obstructing the duodenum itself. In view of this it is believed that excision is better than inversion. However, there will be conditions in which the anatomy will preclude excision. One such situation is the duodenal diverticulum presenting in the periampullary portion of the duodenum. Inversion or excision in this region can produce damage to the common duct or pancreatic duct. Various sidetracking procedures have been carried out for this type of lesion.

When the diverticulum can be excised it should be excised at a point a short distance from the origin of the neck rather than flush with the bowel wall. A two layer closure of the neck of the sac is advocated. Whether the removal of the diverticulum is carried out between clamps by means of the so called aseptic technic or whether it is done by means of the open technic does not seem to make a great deal of difference. This is particularly true if one takes advantage of the local instillation of a Neomycin-Bacitracin-solution at the time of operation.

FIG. 1: Gastrointestinal series revealing pear-shaped, barium filled diverticulum leading off the anterior superior aspect of the duodenum and giving the impression of a barium filled gallbladder (erect film).

CASE REPORT

This 50 year old white woman was admitted to the hospital with the chief complaint of recurrent epigastric pain of approximately 4 months duration. *Family History:* noncontributory. *Past History:* noncontributory except for history of protrusion and bleeding from the rectum. There also was a history of dyspnea and ankle edema in the past. The patient had been hospitalized on different occasions for: appendectomy; suspension of uterus; hysterectomy; thrombophlebitis; and cystoscopy. *Present Illness:* Approximately 6 months prior to the present admission the patient had a total hysterectomy. Postoperatively it was found that there was a right ureteral obstruction. A right uterovesical implant was performed and the patient improved. Subsequent to her discharge from the hospital she developed hydronephrosis and hydroureter on the right.

Approximately 4 months prior to this admission the patient noted weekly recurrent severe attacks of epigastric pain. This pain radiated to both subcostal regions and the right flank as well as the right scapula region and right lower quadrant. There also was some radiation down into the right thigh. Associated with these attacks of pain was vomit-

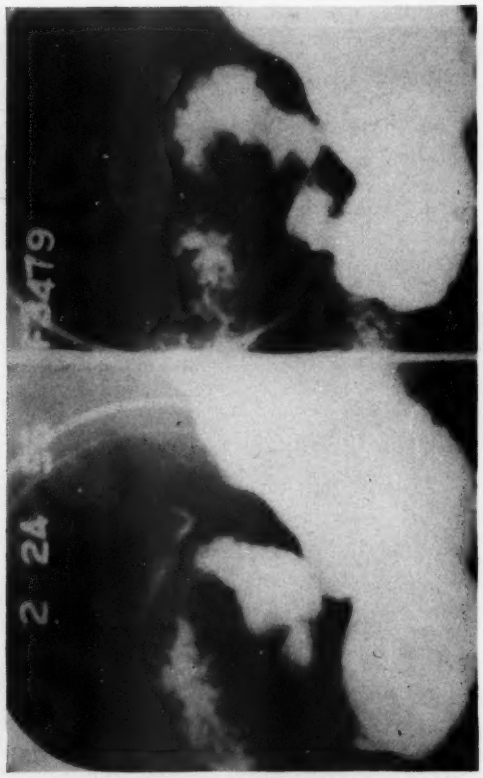

FIG. 2: Lateral view of diverticulum filled with slight amount of barium and primarily air. The diverticulum itself has the appearance of an arrow head in this view with a narrow neck visible at the uppermost end of the diverticulum, (pressure film).

FIG. 3: Lateral view during gastrointestinal series, revealing barium and air within the lumen of the duodenal diverticulum with a narrow, barium filled neck leading off the superior aspect of the first portion of the duodenum (erect film).

ing, fever, and chills. Immediately following one of these episodes, the patient's urine would become dark. There was no specific food intolerance. The last previous attack occurred approximately 1 week prior to admission to the hospital.

The positive features of the physical examination were the presence of bilateral indirect inguinal hernias as well as a right oblique incisional hernia in the right lower quadrant. Sigmoidoscopy examination revealed the presence of internal and external hemorrhoids, anal papillomas and a fissure in ano.

Laboratory Examinations: Serologic test for syphilis; urea; blood sugar; van den Bergh; direct and indirect; prothrombin activity; hematocrit; leukocytes; differential smear; platelets; and urinalysis of catheterized specimen were all negative. Stool examination was negative for the presence of blood. Electrocardiogram examination was negative. Intravenous pyelogram revealed the presence of dilatation of the right pelvo-calycle and ureteral structures. Small bowel roentgenologic series was negative. Gastrointestinal roentgenogram series revealed the presence of a mass 4 cm. in diameter coming off the first portion of the duodenum (figs. 1–4).

Approximately 7 days after admission the patient was taken to the operating room where a resection of a diverticulum of the first portion of the duodenum was carried out. Upon

opening the abdominal cavity the gallbladder was found to be distended and thick walled. It emptied easily and contained no calculi. There were adhesions between the gallbladder and the anterior abdominal wall. The diverticulum measured approximately 5 by 4 cm. and had a neck of approximately ½ cm. in diameter communicating with the posterior superior margin of the first portion of the duodenum. The sac actually was located between the posterior wall of the duodenum and the pancreas. The diverticulum was resected and the duodenum closed primarily (figs. 5, 6). The patient was prophylactically given anticoagulant therapy. Approximately 5 days after the onset of this therapy the patient's hematocrit was noted to have suddenly dropped. It responded quickly to 500 cc. of whole blood. There was no further difficulty following this episode. The patient has been asymptomatic since her discharge from the hospital (approximately 6 months).

Pathologic examination of the resected diverticulum revealed that the mouth of the diverticulum measured approximately 0.2 cm. by 1 cm., in effect being an elliptical opening. The wall itself measured 0.1 cm. in thickness. The wall was somewhat thicker at the neck than it was at the circumference of the diverticulum. The lumen of the diverticulum contained intestinal contents. Microscopic examination of the diverticulum revealed that the

FIG. 4: Flat film of abdomen (recumbent) 3 hours after gastrointestinal series revealing barium and air still within the duodenal diverticulum and a very narrow neck leading off the first portion of the duodenum. Diverticulum is clearly visualized just to the right of the first lumbar vertebra.

FIG. 5: Diverticulum held within the grasp of an intestinal clamp during the operative procedure. The neck of the diverticulum is revealed but has not been completely dissected as yet. What appears to be a second object held within the grasp of the clamp is a reflection in the Deaver retractor.

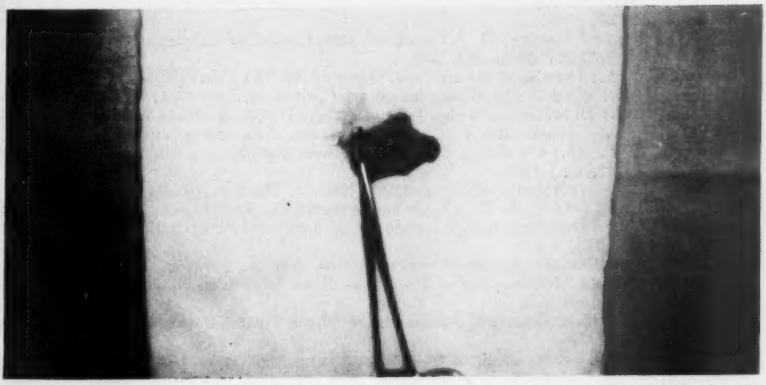

FIG. 6: Photograph of diverticulum following removal. The mulberry-like daughter diverticula are easily seen.

neck of the diverticulum contained some muscle fibers. However, more peripherally, the wall of the diverticulum consisted of mucosa and some muscularis mucosa and Brünner's glands. Thus the section revealed that the diverticulum actually was an out pouching of the mucosal lining. This diverticulum should be included in the primary group.

This case is an example of a symptomatic diverticulum of the first portion of the duodenum presenting a picture of biliary type pain and jaundice as a result of the enlarged diverticulum compressing the common duct.

Results of Surgical Treatment: According to Waugh and Johnston[36, 37] the mortality rate associated with surgical treatment of duodenal diverticula is approximately 10 per cent. This usually is due to complications secondary to the excision of the diverticulum. The literature quotes a 50 to 80 per cent incidence of relief of symptoms following operative treatment of duodenal diverticula[11, 28, 32, 36, 37].

SUMMARY

Duodenal diverticula are reviewed from the standpoint of incidence, age, sex, location, classification, etiology, pathology, symptomatology, diagnosis, complications, treatment, and results of treatment.

A case of a diverticulum of the first part of the duodenum producing symptoms of biliary tract disease, is presented.

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THE MANAGEMENT OF IN SITU CARCINOMA OF THE CERVIX

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Rubin[17] in 1910 and Schottlander and Kermauner[19] in 1912 gave the following morphologic description of a pathologic entity known today as carcinoma in situ of the cervix: Marked anaplasia; disparity in the size, shape and staining quality of the nuclei; loss of cellular polarity; increased mitotic activity; and an intact basement membrane. Various descriptive terminology has been used to describe this lesion—Bowen's disease; superficial, noninvasive, intraepithelial carcinoma; noninvasive, potential carcinoma; and incipient carcinoma.

Until Papanicolaou and Traut's work in exfoliative cytology, the lesion of in situ carcinoma of the cervix was considered to have little clinical significance. However, within the past decade the diagnosis is being made with increasing frequency, and as a result the subject has become one of the most controversial in the field of gynecology. Many factors have contributed to this confusion. Among these are misinterpretation of the histopathology, incomplete or inadequate diagnosis, and the fact that sufficient time has not elapsed to allow proper evaluation of the therapeutic measures advocated.

As a result of the investigations of Smith and Pemberton,[21] Hertig and Younge,[10] Galvin and TeLinde,[7] and Pund and Averbach,[16] evidence has accumulated to prove, beyond a reasonable doubt, that in situ carcinoma of the cervix will become, with the lapse of sufficient time, true invasive carcinoma. This evidence may be summarized as follows: Morphologically, the lesion resembles carcinoma except that the basement membrane is intact; the lesion will progress in a sufficient number of cases from an in situ status to a true invasive carcinoma; the histologic changes of in situ carcinoma can be observed in the epithelium adjacent to obviously invasive carcinoma; the incidence of carcinoma in situ is lower in Jewish than in nonJewish women; the average age in which carcinoma in situ appears is from 8 to 10 years earlier than the average age of invasive carcinoma.

Some investigators have suggested that in a very small percentage of cases this atypical epithelium may revert to normal. This is a difficult assertion to prove. Our own experience has shown that some of these lesions are extremely small and can be removed in their entirety by a single spot biopsy. Hoffman, Farell and Hahn[11] have emphasized that the cells of carcinoma in situ are already malignant. Since irreversibility is characteristic of malignancy, the term carcinoma in situ should not be applied to cases in which the atypical changes regress. We would concur in this opinion.

In the course of a normal pregnancy certain pathologic changes occur in the

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cervical epithelium, and have on occasions been misinterpreted as in situ carcinoma. Danforth,[6] Murphy and Herbut,[14] and Nesbit and Hellman[15] have carried out extensive studies on this problem and have demonstrated characteristic changes in cervical epithelium during pregnancy. Included are hyperacidity of the basal membranes and epidermidalization of the intracervical structures. These changes are superficially similar to the atypical changes of in situ carcinoma but are known to regress and disappear after parturition. Where definite in situ carcinoma has been demonstrated during pregnancy these changes have persisted after delivery.

CASE REPORT

A white woman, aged 27, was first seen at the end of the eighth week of her second pregnancy. Inspection of the cervix revealed no break in the epithelium. The smear obtained for cytologic study was reported as suspicious but the patient refused biopsy. Smears were obtained at 4 week intervals throughout her pregnancy, each showing progressively more and more atypical cells. One week after a spontaneous delivery, a biopsy revealed early invasive carcinoma.

We have no definite proof that this was not invasive at the first visit, but the progressive changes from a suspicious to a strongly positive smear are interesting.

Another source of error in interpretation is the "*atypism*" resulting from inflammatory diseases, among them Trichomonas infestation. Bechtold and Reicher[3] stated, "the greatest single cause of difficulty in distinguishing between benign atypicalitis and malignant atypicalitis has been the Trichomonas infestation".

Inadequate or incomplete diagnosis has added to the confusion, particularly concerning therapy. Schiller[18] stated that 100 per cent of all squamous cell carcinomas of the cervix arise from the squamocolumnar junction. If this is true a biopsy, to be adequate, should therefore include the entire squamocolumnar junction.

Spot or compass biopsies, carried out as office procedures without anesthesia, are helpful but inadequate. They do not include the squamocolumnar junction and do not provide an adequate amount of tissue for pathologic study. A biopsy from one area may reveal what appears as typical in situ carcinoma but this does not prove that this may not have been obtained from the periphery of an invasive lesion.

This phenomenon is here illustrated in figures 1 and 2.

A deep cone biopsy, obtained under anesthesia with a cold scalpel, will provide adequate tissue from the entire circumference of the cervix. It is true that such a routine requires hospitalization, and sometimes a major surgical procedure. However, if the reports in the past are carefully analyzed, it becomes obvious that a great deal of confusion as to therapy and particularly end results could have been eliminated by a cone biopsy.

In spite of the progress made in the last decade in dealing with malignant tumors generally, there has been little change in the salvage rate of invasive carcinoma of the cervix. In 1938 the over-all salvage rate was 26.3 per cent and in 1953, 32.6. It is generally believed that any improvement in the salvage rate

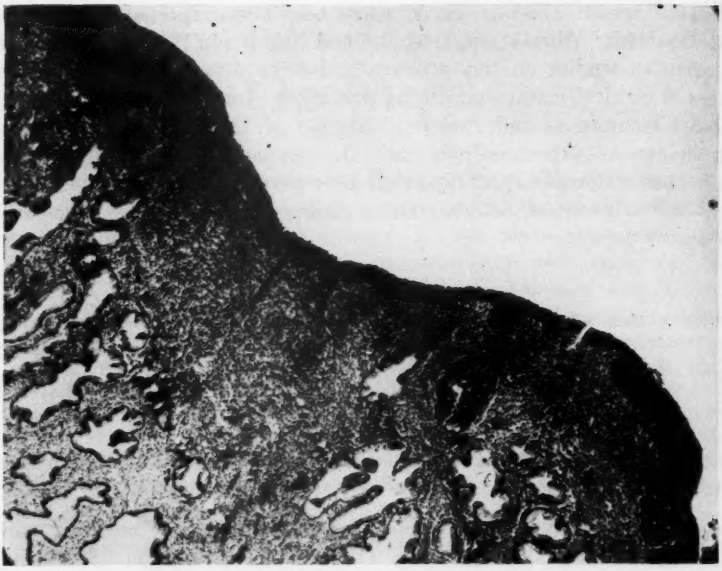

FIG. 1 Malignant surface epithelium with simple extension into glandular crypts and apparently confined to area of excision. Picture compatible with the diagnosis of in situ carcinoma. (Block A.)

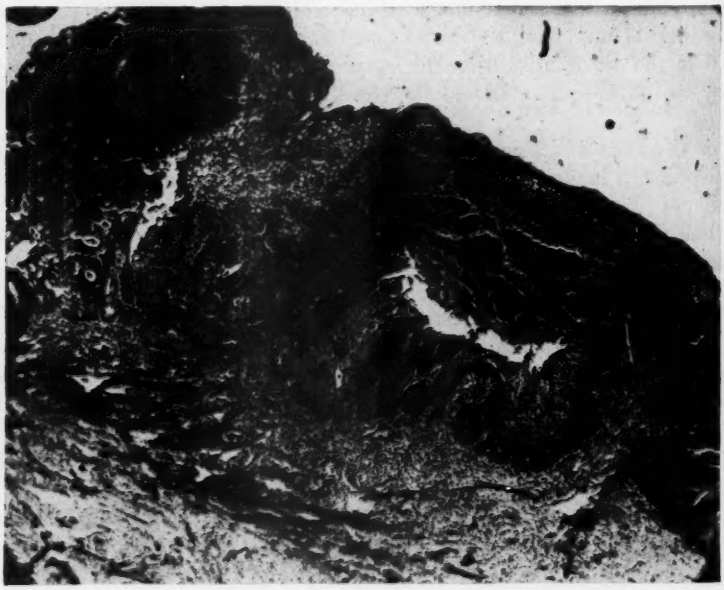

FIG. 2 Squamous cell carcinoma with true invasion. (Block C from the same patient as figure 1.)

depends upon early recognition of the lesion. Since in situ carcinoma will eventually become invasive carcinoma one might assume that adequate therapy at this stage of the disease should lead to practically a 100 per cent salvage rate.

Adequate therapy in any malignant lesion consists in the removal or destruction of the tumor and of as much of the surrounding lymph and vascular bed as possible.

There is little doubt that radiation would offer excellent results in the treatment of in situ carcinoma of the cervix. However, surgery has been the generally accepted therapy. It seems logical that many investigators adopted this approach primarily for the purpose of obtaining adequate material for study.

The surgical therapy suggested has varied from the radical to the ultraconservative—radical Wertheim hysterectomy with pelvic lymph node dissection; total hysterectomy, conserving ovarian function without dissection of the pelvic node; high amputation of the cervix and/or conization and cauterization or both.

It is difficult to evaluate the results of the various procedures because of insufficient lapse of time, and because many of the investigators have included in their discussions cases which appeared as in situ carcinoma on spot biopsy, but which were subsequently proved to be invasive carcinoma after thorough study of the excised uterus. Harris and Peterson[9] have stated that there is approximately a 30 per cent error in the diagnosis of early invasive and preinvasive carcinoma. In TeLinde's[7] report, in 1949, consisting of 75 cases of in situ carcinoma on spot biopsy, 55 cases were subsequently proved to be early invasive cancer. No doubt this large percentage of error influenced the early investigators in their use of the most radical surgical procedures. All of TeLinde's[7] patients were treated by a modified Wertheim hysterectomy and he concludes that any less radical procedures are totally inadequate. With the reduction of the diagnostic error the procedures have become somewhat less radical, and today in the majority of the clinics the lesion is treated by a total abdominal hysterectomy with an adequate vaginal cuff, conserving ovarian function in the younger age group provided there is no associated adnexal disease.

There are many investigators who believe that even less radical procedures may suffice to eradicate the disease. Younge[22] has long advocated the conservative approach to this problem where there is no histologic evidence of extensive invasion of the atypical epithelium into the mucous glands. He reported 27 cases of patients treated by conization without recurrence.

Goldberger and Mentz[8] have suggested that amputation of the cervix may be adequate. They believe that this operation satisfies three conditions: It removes the local lesion; it supplies an ample specimen for histologic study; and it does not interfere with the radical treatment by surgery or radiation should invasion be encountered. Smith[20], Ayre[2], Kimmelstiel[12], Martzloff[13], Achenbach[1], Dahlin, Mussey, and Dockerty[5], and Clark, Russell and Old[4], have suggested that wide conization followed by cauterization may suffice provided the patient will cooperate in a rigid follow-up program.

A cervical smear for cytologic studies is obtained from all adult female patients examined in the Clinic of the Laird Memorial Hospital. Routine biopsy of the cervix is not done. Since cytologic examinations are positive in 90 to 95 per cent of

the patients with malignancy, and because of the simplicity of the technic and the opportunity for repetition, we think that it is a sound diagnostic screening procedure. The results of the cytologic examination are reported as nonsuspicious, suspicious, or positive as the case may be. When the smear is suspicious or positive it means one of three lesions may be present: Anaplastic metaplasia, in situ carcinoma, or invasive carcinoma.

Suspicious or positive smears should never be considered as conclusive evidence of disease. The final diagnosis should be made by a deep cone biopsy. This is obtained under anesthesia and includes the entire squamocolumnar junction. The cone obtained with a scalpel is then cut into from 12 to 18 blocks and many sections obtained from each block, often as many as 150 to 200 sections. If the biopsy specimen shows true invasive carcinoma, the therapy of choice is instituted.

Since adopting this routine we have treated 25 patients with in situ carcinoma. The youngest of these patients was 23 years of age; the oldest 55 years of age. Three patients had had no pregnancies; the remaining from 1 to 10 pregnancies; 1 had had 2 abortions.

The 55 year old patient had undergone a normal menopause at the age of 50. One patient, aged 36, had menometrorrhagia but had an associated glandular cystic hyperplasia of the endometrium. The remaining 23 patients had normal menstrual histories.

This would suggest that in situ carcinoma is asymptomatic.

On examination, 15 of these patients were found to have from clinical observation, a normal cervix. This was the opinion of two or more observers. Normal, as it is used here, means no visible alterations of the epithelium but includes those patients with healed lacerations. The remaining 10 patients presented very superficial erosions, none of which would excite the least suspicion of malignancy.

Therapy of 25 cases of in situ carcinoma of the cervix:

Modified Wertheim Hysterectomy	2
Complete Hysterectomy, Conserving Ovarian Function	8
Amputation of Cervix	3
Deep Cone Biopsy	12

In our early experience, following the diagnosis of in situ carcinoma, the patients were subjected to a total abdominal hysterectomy including an adequate vaginal cuff but conserving the ovarian function in the younger age group. In 9 patients in whom the cone biopsy was followed by hysterectomy, meticulous study of the excised uterus revealed no evidence of any remnants of the atypical epithelium.

Subsequently 3 patients were subjected to a high amputation of the cervix and again no remnants of the atypical epithelium remained following the cone biopsy.

This suggested the possibility that in certain selected cases a more conservative approach may be adequate.

In 11 patients in whom the atypical epithelium did not extend beyond the biopsy and did not undermine the lining of the mucous glands, the cone has been the only treatment.

These 11 patients have been followed from 6 months to 4½ years, with cytologic studies at 3 month intervals. In every instance malignant cells disappeared from the smear following conization and in none of the patients have atypical elements been found on subsequent examination.

In 1 patient the pathologist was not convinced that the atypical epithelium did not extend into the line of the cone excision. Hysterectomy was temporarily deferred. Interestingly enough the atypical cells remained in the smear. She was later subjected to a complete hysterectomy and a small remnant of atypical epithelium was found in the cervix.

We believe that if remnants of atypical epithelium remain following a cone biopsy, the smear will continue to be positive. If such is the case the patient can be treated by more radical surgery, and the short delay will in no way jeopardize her recovery.

In the 9 patients previously referred to, in whom the pathologist could find no evidence of extension of the in situ carcinoma beyond the limits of the cone biopsy, no remnants were found in the excised uterus. However, Harris and Peterson[9] have reported a series of 83 cases of focal in situ carcinoma in which 11 patients or 13.3 per cent, showed residual in situ carcinoma in the excised uterus after cone biopsy. If one assumes that in these 11 patients the biopsy was adequate and the lesion did not extend beyond the limits of the specimen, it is difficult to explain the presence of residual carcinoma.

CONCLUSIONS

In situ carcinoma of the cervix is asymptomatic and not clinically detectable.

Errors in diagnosis may result from inadequate biopsy, misinterpretation of the "*atypism*" because of pregnancy or associated inflammatory disease, or Trichomonas infestation.

If the cytologic examination is suspicious or positive, a deep cone biopsy of the cervix including the entire squamocolumnar junction should be obtained. Spot biopsy as an office procedure is not to be condemned but is inadequate.

If a true in situ carcinoma is found and the lesion does not extend beyond the limits of the cone biopsy, the atypical epithelium does not undermine the lining of the mucous gland, and there is no associated adnexal disease, conization may be considered adequate treatment if the patient will cooperate in a rigid follow-up program.

Such treatment does not deprive the patient of the benefits of radiation or more radical surgery at a later date if the atypical elements remain or recur in subsequent smears.

Eleven patients have been treated by deep cone biopsy and have been followed from 6 months to 4½ years with cytologic smears at 3 month intervals. In all patients malignant cells disappeared from the smear following cone biopsy and in none have atypical elements been found on subsequent examination.

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SURGICAL MANAGEMENT OF PIGMENTED LESIONS

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The presence of pigment adds tremendous importance to any cutaneous lesion. It places the lesion in a special category, one which commands a high degree of respect. In this singular group accurate clinical diagnosis is both difficult and unreliable, and in this group resides one of the most malignant of all tumors. One must not be led into complacency by the concept that "melanomas are luckily uncommon, whereas pigmented nevi abound".[21] Nor should one adopt an attitude of fatalism toward pigmented lesions because of the notoriously high mortality statistics in cases of malignant melanoma. On the other hand, one should keep in mind that the treatment of any pigmented growth calls for utmost caution and care, and that an early careful surgical excision may forestall the future development of a hopelessly disseminated malignant melanoma. In spite of the danger involved, thousands of pigment-containing lesions, clinically regarded as "common moles", are still being treated by divers physical agents, without evidence of complete destruction or regard for pathologic diagnosis. When recurrences or metastases later appear, the procedure is rationalized on the grounds that the treated lesion was "already malignant" and the final result practically predetermined. Such a premise becomes untenable when one realizes that malignant melanomas generally are preceded by the existence of a still-benign pigmented nevus, and that during this quiescent period, before activation and dissemination occur, a safe total scalpel prophylactic removal of the primary lesion is possible. This is considered to be important to the total melanoma picture.

Scope of the problem: Albeit the high degree of malignancy of melanomas should far outweigh any comfort to be gained from statistics indicating low incidence of the disease, evidence indicates that malignant changes in pigmented lesions occur quite frequently and present a challenging problem. In the state of Connecticut, where reliable cancer statistics are kept, malignant melanoma accounts for approximately 1 per cent of the total cancer reported.[16] From 1935 to 1951, a total of 56,908 cases of cancer were reported to the central registry and 576 of these were melanomas. And in 1951, when the population of Connecticut was estimated at 2,049,000, there were 41 reported deaths from malignant melanoma.[13] By deduction, one might estimate that in a city of 100,000 population, 2 persons may be expected to die from malignant melanoma each year. Of a group of 1,016 pathologically confirmed brain tumors recently reviewed by Rix[27] from a large neurosurgical practice, 3.1 per cent proved to be metastatic melanoma. In individual surgical private practice in a city of 100,000 population, the author personally has attended 5 patients through their terminal illness from malignant melanoma during the past 6 year period.

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CASE REPORTS

Case 1. A. P. (M 48) had a "freckle" on left upper arm from birth. Began to itch, and became black in 1946. Local excision was done. One year later a lump appeared in axilla and left axillary dissection was done, with two positive nodes out of 33. One year later developed recurrent axillary mass and had quarterectomy. Three years later died with intracranial metastases.

Case 2. M. M. (F 62). Pigmented lesion left shoulder, present many years, enlarged, became ulcerated, and developed widespread neighboring nodules. Palliative excision and skin graft of left shoulder region was performed in May 1954. Generalized bluish skin metastases and subcutaneous nodules increased. Patient died 10 months later with metastases involving entire viscera including heart.

Case 3. G. B. (M 64) had radium treatment to an interscapular pigmented lesion 12 years previously. In April 1955, developed upper abdominal pain and extensive weight loss. Subcutaneous nodule was excised from midback and was metastatic melanoma. Chest, gastrointestinal and gastric urinalysis roentgenograms were negative, but urine strongly positive for melanin. Within next month patient developed two new black nodules in skin of forehead. Died 1 month later of generalized metastatic melanoma.

Case 4. G. L. (M 29) Bathing trunk nevus since birth. A single warty suprapubic papilloma, traumatized through intercourse, became ulcerated. Excision February 1953, revealed malignant melanoma. Bilateral groin dissection revealed multiple positive inguinal nodes bilaterally. Died within 1 year with extensive pulmonary metastases.

Case 5. O. T. (M 50). Small brown mole on right deltoid region present for many years. Slowly grew and became raised and darker. Struck it with a board and it bled and ulcerated. Was excised in 1954. One year later developed multiple subcutaneous nodules over body generally and an enlarged nodular liver. No adenopathy ever appeared in right axilla or in any node areas. Patient died at home 3 months after the appearance of nodules of generalized melanocarcinomatosis.

During the same period, 8 additional instances of malignant melanoma have been seen in private patients, into whose surgical management participation has been partial or complete. Two patients with malignant melanoma of the upper arm have had excision and axillary dissection: one, (male 30), with negative nodes, is living and well after 6 years; the other, (male 55), with one positive node, died 2 years later with clinical diagnosis of cerebral hemorrhage. A female (32) with melanoma of the scalp is living 5 years after therapeutic neck dissection, and 6 months after removal of an intracranial metastasis. A male (82) with malignant melanoma of the sole of the foot died from intercurrent disease 2 years after excis on and skin graft, without clinical evidence of metastasis. A female (83) with malignant melanoma of the face is living and well 5 years after excision and skin graft. A male (39) with malignant freckle (fig. 3) of the face is living and well 1 year after excision and skin graft. A male (36) is living without evidence of disease 7 years after excision of a superficial melanoma of the back and 5 months after therapeutic axillary dissection. One male (66) with melanocarcinoma of the right malar region, with satellite nodules, refused treatment and died 3 years later of unverified cause. This individual experience tends to confirm the impression that "malignant melanoma of the skin is not a rare neoplasm".[2]

In addition to melanocarcinoma, other malignant variants are apt to arise in pigment-containing skin lesions. As examples, the author has encountered pigmented basal cell carcinomas, malignant change in the verrucous nevus, Kaposi's

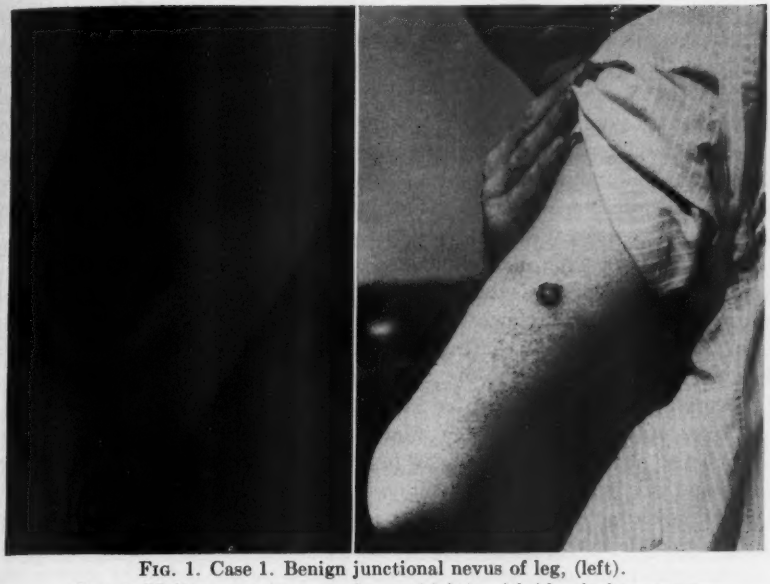

FIG. 1. Case 1. Benign junctional nevus of leg, (left).
Case 2. Malignant melanoma of arm, (right), with identical appearance.

sarcoma, and leukemia cutis which had the clinical appearance of a common intradermal nevus. These diagnoses were brought to light through excision and microscopic examination, and would otherwise have gone unrecognized. This group of lesions carries a lesser degree of malignancy than that of melanocarcinoma, but their diagnosis and treatment was none the less vitally important to the patient.

Clinical Diagnosis: Surface pigmented lesions are difficult to diagnose clinically with any degree of accuracy (fig. 1). The most prevalent of the group are the so-called nevi or moles. The intradermal nevus or "common mole" usually is raised from the surface, rounded or domed shaped, with smooth contour, and often contains hair. Its color may range from that of normal skin to many gradations of tan and brown. Usually it is lighter in color than the typical junctional nevus, which ordinarily is flat, hairless, and often is quite deeply pigmented. Unfortunately, junctional findings are not limited to the typical junctional nevus, for about 12 per cent of the raised, harmless appearing, intradermal nevi contain junctional foci[5], and are called compound nevi. The juvenile melanoma also is apt to be hairless and smooth, but usually is larger and more elevated than the junctional nevus commonly seen in childhood. The "blue nevus" is a smooth, slightly raised, hairless, blue or blue-gray shiny lesion located often on the dorsum of the extremities or on the face. These have become malignant in only a very few verified instances. Allen[5] has reported 6 cases of malignant blue nevi, and Montgomery and Kahler[20] listed only 9 cases as appearing in the literature up to 1939, but emphasized that these could become malignant when subjected

to prolonged and repeated trauma or irritation. Keeping in mind that the malignant melanoma is believed to arise in a pre-existing nevus, it is important to scrutinize all nevi very closely. A great variety of other pigmented lesions exist, and may closely resemble either nevi or melanocarcinomas. These lesions include the pigmented papilloma, seborrheic keratosis, pyogenic granuloma, pigmented basal cell carcinoma, sclerosing hemangioma, dermatofibroma, angioma, sebaceous cyst containing blood, intradermal or subdermal hematoma, Kaposi's sarcoma, neurofibroma (von Recklinghausen), leukemia cutis, glomus tumor, and even an occasional foreign body tattoo mark.

While a full-blown melanocarcinoma with satellite manifestations may be recognized at a glance, it is the premalignant or early quiescent melanoma whose recognition and prompt removal may mean so much to the patient. Unfortunately, most of these defy clinical diagnosis, and early malignant changes can be detected only with the aid of the microscope. Without the pathologic specimen, differential diagnosis of pigmented lesions is fraught with errors and pitfalls.

The precursory pigmented lesion: Malignant melanoma is considered by many observers to arise in a precursory or pre-existing pigmented lesion. The recognition and safe removal of these still quiescent lesions should have a great influence on the ultimate prognosis. Reports indicate that in the majority of instances the malignant lesion has been observed by the patient to be preceded by a "mole". Patients with malignant melanoma who definitely remembered the pre-existence of such a pigmented lesion made up a high proportion of the total cases in several reported series: 84 per cent (Affleck)[4]; 80 per cent (Driver and MacVicar)[11]; 67 per cent (Lund and Ihnen)[15]; 65.4 per cent (Webster, and associates)[32]; and 61 per cent (Ackerman)[1]. Daland and Holmes[8] reported only 18 per cent of patients having observed such a precursor, but their percentage seems less reasonable when one considers how easily a person may overlook the presence of a pigment spot unless it is exposed to easy view, or unless it has begun to produce subjective symptoms. Actually, there are many surface areas of the body which are obscured from casual self-observation and only with the help of mirrors or other observers would one have knowledge of the presence of such a lesion. Hall, and associates[14] stated that "although previously unnoticed, it is possible that in every instance melanoma develops upon the site of a pigmented nevus". Allen[5] reported that 89.2 per cent of 362 studied malignant melanomas had origin and were superimposed upon a junctional nevus. Unfortunately, in another 286 cases, almost half of the total number reviewed, the primary lesion was not available for histologic study, having been destroyed by cautery, irradiation, or other agents. Masson[17] stated that "it is beyond a doubt that a nevus quiescent for a considerable time may be the original site of a melanoma. Bearing in mind the universe number of all varieties of existing nevi, this eventuality may be considered rare. Nevertheless, it is frequent enough and the consequences serious enough to justify consideration."

Pigmented Lesions to be Excised: It would appear that the indications for surgical excision of a pigmented lesion should be extended beyond that commonly practiced. In general, any such lesion which is brought to the attention of a phy-

sician by the patient or his relatives should be given the benefit of a diagnostic excision. Every lesion which is heavily pigmented or is ulcerated cannot be diagnosed with certainty and should be totally excised. More particular attention is usually given to the nevi which appear to be of the junctional type, yet one cannot safely pass over the typical intradermal nevus or "common mole", for some 12 per cent of these contain junctional foci.[5] Indeed, even the pure form of intradermal nevus has been observed to become malignant.[29] Pigmented lesions located on the lower extremities, the genitalia, the soles or palms, the hair line near the temple, or the subungual regions should be excised, for malignant melanomas are more prone to develop in such areas. All regions exposed to repeated shaving, including the extremities and axillas in females, should be free of pigment-containing skin elevations. Projections known to be traumatized by combing, picking by children, or handling of any sort should be prophylactically removed. Pigmented nevi subjected to pressure and friction of shoes, straps, belts and the like deserve to be excised. Lesions which happen to be in folds or creases or flexor surfaces and thereby become involved in bending motions also warrant removal. Moles from which the patient habitually pulls out hairs, for cosmetic reasons, should be spared this repeated trauma and should be excised. Any nevus which is darker than tan or medium brown should be removed because it is much more difficult to notice future changes in color as the darker shades are approached. In fact, Scanlon[28] is of the opinion that deepening in color, ulceration, or bleeding represent not an early sign of malignant change, but actually are late manifestations and precious time has already been lost. Any lesion which itches, tingles, develops a splotchiness or darker spots within itself, or develops a pale halo around itself should become immediately suspicious. If a lesion enlarges or raises itself above the surface so that it becomes more subject to irritation or trauma,[10] it should be removed without delay. Should the decision be made not to remove a lesion called to his attention, it is then the responsibility of the physician to maintain accurate observation at regular intervals, for ordinarily the patient cannot be expected to notice early changes as readily as the physician.

The Diagnostic Excision: If one waits until a pigmented lesion shows gross evidence of becoming malignant, it may already be too late for a complete cure in many instances. The extended use of a safe method of excision for diagnostic purposes should bring about an earlier and more favorable influence on the melanoma picture. It has been suggested that only general anesthesia be employed in the excision of melanocarcinomas.[12] Such a policy has merit in the typical case, but does not fit well into a program where one aims to excise lesions at a much earlier stage, before they take on definite malignant features. The careful injection of local anesthesia into the skin widely around the lesion provides a painless means of excision of such lesions and avoids delays and postponements for want of general anesthesia. The inner rim of the wheal is not allowed to contact the periphery of the lesion, and the injecting needle is obviously kept well away from the tumor itself. No infiltration is necessary beneath the lesion, and need only be in the surrounding skin, for the subcutaneous tissues are relatively insensitive to pain. In this way there is no risk of disturbing or distending blood vessels or

lymphatics beneath the lesion. A straight-down incision well into the fat, without beveling, made at least ½ centimeter beyond all surface borders, removes an ellipse of skin and fat with the lesion in the center, untouched by any instrument or solution. The margins of safety are confirmed by the pathologist, in all axes and depths, and once the adequacy of excision has been verified, there should be no fear of local recurrence. If the margins should show questionable adequacy, or if junctional foci appear at the edge of the specimen, then a wider re-excision of the entire field is immediately performed. Closure of the defect is never a problem because of the easy procurability of a split or full thickness skin graft, also obtained under local anesthesia. Allen[5] attributed most local recurrences to activated junctional foci at the margins of previous removals, so one's excision must extend beyond any such microscopic foci. Unfortunately, the knowledge of an adequate removal is lacking when the lesion has been destroyed by physical agents or excised with the hot cautery. Amadon[6] studied 27 lesions treated with the electric needle, in which 100 per cent recurred locally or metastasized, and he believed that the tumor cells were steamed out into peripheral venules and lymphatics, and rapid spread of the growth was promoted in this manner.

Although some authors believe that an incisional biopsy should never be done in the case of suspected malignant melanoma,[19] it is probable that such a procedure is relatively safe if promptly followed by total removal of the lesion including the entire field of the biopsy. Actually such a biopsy is usually redundant[31] because total removal ordinarily should follow, even though the lesion proves benign. It is not often that pigmented lesions are too large to be totally removed and the defect closed by suture or skin graft. Furthermore, the microscopic diagnosis may be more reliable if the pathologist has had the privilege of studying

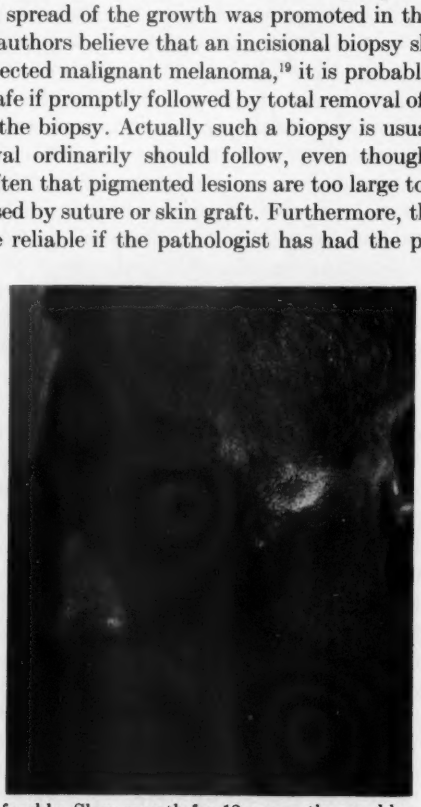

FIG. 2. Malignant freckle. Slow growth for 13 years, then sudden development of black raised center., Patient living and well after radical excision and graft.

the entire specimen (fig. 2). A total excision obtains both diagnosis and treatment simultaneously, and often at a time when there is still a golden opportunity for complete cure.

Pigmented Lesions in Children: The most common pigmented lesions seen in children are the junctional nevi, and these are uniformly benign, at least until after puberty, with very few exceptions. At the same time, a great many patients with malignant melanoma have noticed a pre-existing lesion as far back as they can remember, which means that in many instances the lesion was present during childhood. Driver and MacVicar[11] observed that 41 per cent of 60 patients who had malignant melanoma gave a history of a pre-existing pigmented lesion present at birth or soon afterwards. During these early years of life a great opportunity presents itself to safely remove a great many potentially dangerous lesions through a prophylactic approach. Pack[25] related having had the "heartbreaking experience of treating too many young girls and boys aged 14–20 years for malignant melanomas that could have been prevented by the prophylactic excision of benign precursory nevi in childhood." These excisions should include at least the darker nevi and those located in the danger areas described for adults. It is perfectly feasible to do most of these scalpel removals under local anesthesia, which children tolerate quite well. Or when general anesthesias are anticipated for purposes of tonsillectomy, herniorrhaphy, and the like, one should use this opportunity to remove all indicated nevi at that time.[3] Special instances may occur where planned multiple-staged procedures may be necessary in order to remove extensive congenital nevi which later are apt to become malignant. In the case illustrated (fig. 3) such a procedure, although formidable and challenging, might well have been a life saving measure.

FIG. 3. Congenital bathing trunk nevus. Became malignant and caused death within 1 year.

Pigmented Lesions and Pregnancy: It has been widely observed that pigmented nevi may become darker or increase in size during pregnancy. Increased cellular activity takes place within the nevus and it is important, especially at this time, that there be no tampering with physical agents, which often bring about only partial destruction of the nevus. Rapid recurrences are much more likely to develop during pregnancy, and have a greater potentiality toward malignant change. An example of this was seen recently in a 19 year old white female. During her first trimester of pregnancy a raised medium brown mole of the temple, clinically an intradermal nevus, increased in size and was treated with cautery by a dermatologist. A few weeks later a coal black raised nodule appeared in the center of the saucered out smooth scar area and continued to grow rapidly. Radical excision of the entire field was carried out. Microscopically, the cells were deeply pigmented, pleomorphic, disarranged and scattered widely throughout the dermis and underlying fat. Diagnoses of several pathologists have ranged from that of definite malignant activation to the recurrence of a benign nevus whose activity increased as a result of hormonal stimulation. The final answer in this case may rest with the long follow-up of the patient.

Pack[23] has stated that he has never seen a patient who developed malignant melanoma during pregnancy survive for any length of time. There are indeed many recorded instances of rampant metastases, including transmission through the placenta with ultimate fatality for both mother and child.[9] A survey of all pigmented nevi should be included in every routine prenatal examination. During this critical period, if changes are noted to occur in an individual nevus, beyond the increase in general pigmentation observed in the areolas and elsewhere, careful diagnostic excision should be done, and may provide valuable information, at little or no risk to the patient.

Management of Malignant Pigmented Lesions: When and *how* the primary lesion is treated may be the most influential of all factors in the therapy of melanomas. In studying 100 cases of malignant melanoma referred to the Holt Radium Institute between 1933 and 1942, Tod[30] was of the opinion that 34 patients had been led to rapid death with recurrence or metastasis as a "result of meddlesome and incompetent treatment". Hall[14] considered 59 patients to have received inadequate primary treatment, and only 4 of these patients were living after 5 years. Electrodesiccation was the method used in the majority of these instances. Gage[12] reported that 60 per cent of the patients that he sees give histories of once having had a black mole treated with an electric needle.

Although an early total primary removal is of utmost importance in every case, one's efforts at cure must not cease when the microscopic sections reveal malignant melanoma. McCune and Letterman[18] stressed the importance of prophylactic gland resection in all cases of melanocarcinoma, and they report microscopic metastases in 50 per cent of patients in whom prophylactic node dissections were performed. Of 7 such patients, 2 are still living and well after 10 years. Pack[22] reported minute foci of metastasis in ⅔ of a group of cases of melanoma of the extremities when the nodes were clinically negative. Lund and Ihnen[15] have stated that there is still no controlled data to support the thesis that prophylactic

node dissections are worthwhile insofar as cures are concerned, but they express a personal belief that the procedure is indicated if the regional lymph nodes are in predictable and accessible areas. It would seem to the author that the value of prophylactic dissections applies to melanomas as with other highly malignant growths. Whether the node dissection should be done simultaneously or 3 or 4 weeks later is a question as yet unanswered. In practice, node dissections may unavoidably be delayed until permanent paraffin sections can confirm a diagnosis which might have been inconclusive on frozen section. Pack's[26] technic of excising intervening skin and fascia between primary and node areas deserves serious appraisal, but is often impractical when long distances are involved.

The value of extended radical procedures, such as quarterectomy, which occasionally must be employed in order to remove far advanced metastases, is still rather unconvincing, and may represent merely a last ditch effort in the treatment of a disease that has already escaped beyond apprehension. Such mutilating and disabling procedures certainly should not be employed in the primary treatment of melanocarcinoma of the extremities, and become indicated only when it is impossible to encompass the metastases by lesser procedures. One should not fail to offer the patient every opportunity for possible cure, but it is easily apparent that the chasing down of metastases is too often unfruitful in the case of melanocarcinoma. Reviewing the end results in 1,190 cases of malignant melanoma, Pack, Gerber, and Scharnagel[24] have reported 14.1 per cent of patients with positive nodes living 5 years without evidence of disease, as compared with 40.5 per cent when lymph nodes were negative. They assume that the remaining 60 per cent of the second group were lost through blood stream metastases. One must also keep in mind that 5 year survival, particularly in cases of melanocarcinoma, is not equivalent to cure.

It is apparent that great room for improvement exists in the treatment of melanomas, and it may be that a well planned early "frontal" approach to the problem may help to bring about more favorable statistical results. And although one unfortunately cannot measure in numbers of cases just how many melanomas are thereby prevented or cured, the early prophylactic approach deserves continued serious consideration.

SUMMARY AND CONCLUSIONS

The proper surgical management of pigmented cutaneous lesions is of tremendous importance. The incidence of malignant melanoma is significantly high, and in most instances a pre-existing lesion is definitely implicated. Diagnosis of surface lesions containing pigment is unreliable without the aid of the tissue pathologist. The value of diagnostic excision is emphasized, and indications for its extended use are presented. Prophylactic excision of nevi is discussed, and its special applicability in children is presented. The early surgical consideration of all pigmented lesions will exert a favorable influence upon the melanoma problem.

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DISCUSSION

Dr. Lockhart is to be congratulated upon the presentation of a comprehensive and practical paper on the problem of pigmented lesions. There is seldom a day that passes in practice that one is not confronted with decisions regarding the removal of such lesions.

The initial surgical attack upon any pigmented lesion is by far our most important operation at this time. We have all been disappointed with many of our secondary surgical procedures on patients with malignant melanomas. To reiterate, this excision should be done courageously if there is any suspicion that the lesion may be malignant. The excised borders should be much greater than in the case of squamous or basal cell carcinoma. That this initial excision is most important is borne out by the fact that there is about a 20 per cent local recurrence rate with these lesions. Allen speculates that this high local recurrence rate is due to failure to excise not just the nevus but the surrounding junctional cells as well.

The etiology of the activation of the junctional nevus into a melanocarcinoma is as yet unknown, but it is an established fact that in a person having a proved melanocarcinoma the development of a second primary melanoma occurs with twice the frequency that it does in a person with no previous history of melanoma. The second melanoma was once thought to represent a metastatic lesion, but now, due to refinements in their histologic study, most pathologists feel secure in distinguishing between a metastatic lesion and a second primary melanoma. For this reason, once a melanoma has been removed, frequent meticulous examinations should be carried out and any second suspicious lesion widely excised.

The danger of pigmented nevi on the feet and genitalia has been stressed. This can partially be explained by the fact that the majority of pigmented nevi in these locations are of the junctional variety, which is the precursor of the melanocarcinoma.

The effect of trauma has never been proved to be a factor; however, many authors report that ulceration of a melanocarcinoma invariably carries a fatal prognosis.

The advisability of prophylactic node dissection similarly can be debated. But, to reaffirm what Dr. Lockhart has said, such an attack remains at the present our only method of eradicating the spread of this very malignant lesion.

Finally, one should always remember that with malignant melanoma, between 12 and 15 per cent of fatalities occur after the 5 year period.

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CARCINOMA OF THE THYROID IN CHILDREN

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Carcinoma of the thyroid in children is a disease that is infrequently seen. Winship and Chase[24] have collected 285 cases. The first published case report was by Ehrhardt[6] in 1902. The incidence of this condition is said to be increasing, especially in the United States, and this is not considered to be due to better diagnosis or case finding.

Authors discussing childhood thyroid carcinoma have taken different upper age limits (10–25 years). In the series by Winship and Chase the age span was from birth to 15 years. The diagnosis has been made from age 4 weeks to 14½ years, 5 children having a tumor noted at birth. The incidence of childhood carcinoma in nontoxic nodular goiters has varied from 19.3 to 52.6 per cent[24, 10, 11] the average being 29 per cent, which is higher than in adults. Many of the major clinics report that 1 to 6.5 per cent of all thyroid carcinomas occur in children.

CASE REPORT

A 9-year old white girl was admitted to the hospital on May 10, 1955 because a mass was noted in the region of the left lobe of the thyroid 10 days previously. The child had a normal birth and development. She had been given x-ray therapy for an enlarged thymus at 6 months of age. Adenoidectomy was performed at 4½ years of age. Tonsillectomy and adenoidectomy was performed at 6 years of age. A benign nevus of the left thigh was removed 6 months previously. The family history was negative. Physical examination was negative except for a firm, discrete mass, approximately 1.5 cm. in diameter just anterior to the lower border of the left sternocleidomastoid muscle. The mass was not attached to the skin or sternocleidomastoid muscle, but moved with deglutition. Along the anterior border of the sternocleidomastoid in its mid and upper portions were 2 firm, freely movable, discrete lymph nodes approximately 0.5 to 1 cm. in diameter. There was slight generalized lymphadenopathy. Chvostek's sign was positive bilaterally. Roentgenogram of the neck and chest, and a barium swallow showed no evidence of substernal thyroid, compression of the esophagus or metastasis. The analysis of blood, including calcium and phosphorus, and the urine examination were normal. The uptake of radioiodine‡ by the thyroid was that of a low normal gland. There was half as much radioiodine in the site of the left thyroid nodule as in the region of the isthmus. There was no extra thyroid localization of radioiodine. Under endotracheal anesthesia a left thyroid lobectomy with removal of the isthmus was done. Frozen section was reported to show "Follicular adenocarcinoma." Total thyroidectomy and left radical neck disection was carried out. The patient withstood the procedure well and left the operating room in good condition. Prophylactic tracheotomy was done. The recurrent laryngeal nerves were visualized and what was identified as parathyroid glands were left behind. Postoperatively no signs of tetany or respiratory distress developed. Blood calcium

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‡ This tracer test with 16 microcuries of radioiodine (I^{131}) and tissue measurements was performed and interpretated by Dr. Elliott Levi and his associates, Associate Attending Physician, Radioisotope Laboratory, Department of Radiology, Sinai Hospital of Baltimore, Inc.

and phosphorus remained within normal limits. The tracheotomy tube was removed 4 days later. The pathology report* stated that:

"The resected left lobe of the thyroid gland weighs 5.8 grams and measures 2.8 by 1.8 × 1.4 cm. On section the cut surfaces present a well circumscribed, tawny, lobulated nodule measuring 2 by 1.5 cm. It occupies approximately ⅔ of the entire left lobe. Lymph nodes which vary in size from 3 by 2 by 2 mm. to 1.3 by 7 by 1.0 cm. were in the neck dissection. Several are soft; on section their cut surfaces are tawny and smooth. One embedded in the soft tissue below the external jugular vein measuring 1.2 by 0.5 by 0.5 cm. is firm. On section the cut surfaces are a homogeneous creamy tan. Diagnosis: Follicular adenocarcinoma of left lobe of thyroid. No involved lymph nodes were found. Acute and chronic hyperplastic lymphadenitis."

Radioactivity measurements of the specimen revealed the tumor mass in the left lobe of the thyroid to have approximately ½ of the radioactivity of the right lobe. The cervical nodes showed no radioactivity.

A week later radioiodine uptake was repeated. The survey revealed no residual thyroid tissue. The patient was discharged on thyroid medication.

Follow-up 6 months later revealed normal development. A radioiodine uptake showed no evidence of any thyroid tissue or abnormal uptake. Roentgen examination revealed no bony metastasis. Follow-up 1 year after surgery revealed normal development and no evidence of metastasis.

Pathology

Pathologists today report that thyroid carcinomas often contain more than one cell type, with one type predominating. Some of the metastases differ from the original cell type,[5, 12, 16] some have more than one histologic type in the metastases. In children the percentage of occurrence of different cell types is similar to that in adults. The papillary and follicular types are seen more frequently. A papillary element is noted in 54 to 65 per cent, purely papillary tumors are seen in approximately 16 per cent. Up to 69 per cent have a follicular element, 20 to 29 per cent being purely follicular. About 15 per cent are undifferentiated carcinomas. No Hürtle cell carcinomas have been reported in children.

When first seen in children 64 to 77 per cent had cervical lymph node metastases[11, 13, 24] (18 per cent bilateral); 15 to 24 per cent had pulmonary metastases, and 3 to 5 per cent had osseous metastases. In the cervical lymph node metastases most often the deep jugular chain has been involved. Most of the pulmonary metastases were asymptomatic. In one patient calcification was seen on roentgenogram in a carcinoma.[13] Three patients were reported to have benign colloid adenomas on the opposite side.[22] A thyroid carcinoma has been seen in a thyroglossal cyst in a 6 year old boy.[13]

The papillary type tends to recur locally, and in the regional lymph nodes; it sometimes metastasizes to the lungs. The follicular type usually does not recur locally or involve the regional lymph nodes, but does metastasize to bone early and lungs later.[7] The clinical entity of the single nodule has been shown many times to be a multinodular goiter pathologically. Out of a group of 155 supposed

* This is the report of Dr. Tobias Weinberg, Pathologist-in-Chief and Director of Laboratories, Sinai Hospital of Baltimore.

single nodules, 101 were pathologically multinodular, 11 per cent being carcinomatous.[12] It is well known that some thyroid carcinomas, especially the papillary type, have a very slow progressive course, over a period of many years.

Etiology

Of 116 children with thyroid carcinoma, 16 had thymic irradiation in infancy.[24] Simpson[20] followed 1400 patients having thymic radiation. Seventeen subsequently developed a malignant disease; 6 developed a carcinoma of the thyroid. Duffy and Fitzgerald[5] reported 10 cases of thyroid carcinoma in patients in childhood and adolescence with thymic irradiation between the ages of 4 to 16 months. They suggested the possibility of a thyroid thymic endocrine interrelationship. Langmann and Bruch[14] and Buchwalter and Meridith[1] each reported a childhood carcinoma of the thyroid with thymic irradiation in infancy. Others[13, 17, 22] believed thyroid carcinomas arise in pre-existing adenomas or are congenital. Potter and Morris[17] think puberty is a stimulus to malignant degeneration. Although there are more female child thyroid carcinomas than male (64 per cent female), a thyroid nodule in a male child is more likely to be malignant.

A multicentric origin[10, 12, 15] has been reported by many, some reported bilateral. This is especially true in papillary tumors

Thyroid carcinomas have been reported in 2 children who received thyroid extract for suspected cretinism in infancy.[13, 17] Most observers believe that geography has nothing to do with thyroid carcinoma and that the main reason a large number of cases is reported from one area is because of local medical interest.

Symptoms and Signs

In the usual case an asymptomatic cervical mass is felt either in the thyroid or in a lateral region. Enlarged cervical nodes should be biopsied, especially ones showing rapid growth. Pressure signs such as hoarseness or dysphagia occur late. The delay from the first symptom or sign until the diagnosis was made has varied from 1 month to 11 years, the average being slightly over 2 years.

Treatment

It is difficult to compare the different types of therapy since the follow-up often is poor, the terminology used does not always indicate the type of operation clearly and the natural history of the disease frequently is a long one. In one reported case a patient had further surgery 26 years after the primary procedure. Crile[3] believed that at least 20 years must pass before cure rate for thyroid carcinoma can be evaluated. In a series of 285 collected cases[24] 92 per cent of the patients were treated surgically, 39 per cent having a total or subtotal thyroidectomy, 21 per cent a lobectomy, 30 per cent a radical neck dissection (10 per cent bilateral). Surgery for recurrence or residual tumor was carried out in 30 per cent of those treated surgically. Forty-two per cent received x-ray therapy; 19 per cent received radioiodine, and about 2 per cent had radium therapy. The modern

concept of the biologic behavior of many of these carcinomas is that metastatic seeding takes place early, but it takes time before the metastases become clinically apparent. The reason for this is not known.

Surgery

Considering that multicentric foci of origin occur, and that metastatic seeding within and without the gland can occur early, a total thyroidectomy should be done. That a unilateral radical neck dissection should be carried out is considered wise,[2] others prefer either a bilateral neck dissection or at least a regional lymph node dissection to the opposite internal jugular vein. MacDonald and Koten[15] reported that if a focus of metastatic carcinoma is found in a cervical lymph node, in 1 out of 7 instances, the primary lesion will be in the contralateral lobe. Some observers[5, 21] feel a hemithyroidectomy and neck dissection is the treatment of choice, to be followed by x-ray therapy. Horn and Ravdin[11] stated that when lateral aberrant thyroid is found, a radical neck dissection and hemithyroidectomy including the isthmus should be done only if nodes are palpable. Others state that neck dissection should be carried out only in the papillary or follicular cell types.[22] Crile[3] stated that for papillary carcinoma lobectomy and removal of the cervical metastatic lymph nodes alone should be done, classical radical neck dissection not being necessary; in nonpapillary carcinomas his treatment is lobectomy and removal of the ipsilateral internal jugular vein in continuity.

If carcinoma is suspected, a lobectomy and frozen section should be done so that definitive surgery can be done at that time. If extensive invasion is found, as much thyroid as possible should be removed in an attempt to aid possible future radioiodine or x-ray therapy. Many believe surgery should be attempted for recurrence. In a few children in whom subtotal thyroidectomy or unilateral lobectomy was done, a multiple colloid adenomatous goiter developed in the remaining thyroid tissue.[8]

After total thyroidectomy in children, thyroid extract is apparently adequate for normal development. Langmann and Bruch[14] have done metabolic studies in such children.

Radiation

X-ray: The older literature has numerous examples of x-ray therapy for lymph node or pulmonary metastases.[8, 14, 17] Repeated courses of x-ray have been successful in some instances for recurrent metastases, lymph node and pulmonary. One patient developed an osteochondritis of the cervical spine. X-ray therapy also has been used on the primary lesion successfully. It is noted that most of the cases responding to x-ray were of the papillary type. X-ray has been used prophylactically after surgery.

Radium: Local radium on cervical metastases or local implantation of radon seeds has been followed by disappearance of these metastases[8, 13] in some reported cases.

Radioactive Iodine: Most of the experience with the use of radioactive iodine[4, 7, 16, 18, 19] is limited to adult thyroid carcinomas. In 1938 it was shown by Hertz,

Roberts, and Evans[9] that the mammalian thyroid was capable of selectively accumulating radioactive iodine following its intravenous injection as aqueous sodium iodide. The indications for radioactive iodine therapy are:

1. The tumor was not removable by a competent surgeon.

2. The tumor was capable of concentrating enough radioactive iodine to exert a cancericidal effect.

3. The calculated total body irradiation was within range of safety.

Important is the total removal of all thyroid tissue to make the metastases more avid for radioactive iodine. In some, thiouracil, with the thyroid in or out, will help increase the avidity of the metastases for radioactive iodine.

The limitations of radioactive iodine therapy are:

1. A relative or absolute lack of natural avidity for radioactive iodine and variability of function of tumors which do concentrate radioactive iodine.

2. Iatrogenic impairment (patient was given iodine containing compound or radiation).

3. Damaging effects of radiation on normal and vital tissues (occasional amenorrhea or bone marrow depression has been reported).

It is important to stop thyroid extract at least 6 weeks before radioactive iodine is given. The patient will show varying amounts of hypothyroidism. When thyroid stimulating hormone (TSH) is given, it is stated that it is not necessary to stop the thyroid extract. The use of TSH to cause metastasis to take up radioactive iodine in cases where it has not been taken up has failed.

It is believed that the total removal of the thyroid with the administration of thyroid extract will eliminate the stimulating effect of the pituitary on the metastases. Radioactive iodine has been used after thyroidectomy in an attempt to make certain that all thyroid tissue malignant or normal is destroyed.

The follicular or papillary cell types are more likely to pick up radioactive iodine. About 10 to 45 per cent of thyroid carcinomas have been reported to accumulate radioactive iodine. The lowest percentages are derived from Geiger counts of the specimen and the highest percentages are obtained by radioautographs. The average obtained by Geiger counts of the specimen is about 20 per cent. Cases have been reported where the primary tumor picked up little radioactive iodine, but the metastasis picked up a large amount. Some of the results of radioactive iodine have been quite dramatic, especially in the presence of osseous metastasis. Many years must pass to evaluate the length of the therapeutic effects of radioactive iodine. Some patients have shown complete clearing of lesions in bone or lung (up to 4 years at time of report).[12] Others have shown merely lack of progression.

Results

Comparison of results of different types of treatment is difficult mainly because of the natural life history of the disease. Although it can kill rapidly, especially the undifferentiated type, many patients have a long history and recurrence or metastasis may not show up until decades have passed.

Of 197 patients followed,[24] 74 per cent of those living over 10 years had a

papillary element, 18 per cent were pure follicular, 8 per cent were undifferentiated. Sixteen and seven-tenths per cent died of the disease (65 per cent had a papillary element; 22 per cent had a follicular element; 13 per cent were undifferentiated). It was believed that the prognosis in the child is the same as that in the adult. Others[11, 22, 23] have found similar results in the mortality rate varying from 16 to 20 per cent, although some are alive with arrested disease. It is interesting that even though metastasis or local recurrence is present, in many patients there is no striking disability.

Summary

The literature on carcinoma of the thyroid in children is reviewed.

Approximately 1 to 6.5 per cent of thyroid carcinomas arise in children.

There are a significant number of cases of thyroid carcinomas in children who had received thymic irradiation in infancy.

The role of surgery, radioactive iodine and x-ray therapy are discussed. The proposed therapy is total thyroidectomy and unilateral neck dissection (bilateral if metastases are found on the contralateral side). Subsequent surgery, radioactive iodine or x-ray therapy are used, in that order, when feasible for recurrence or subsequent proved metastasis.

The average mortality is 16 to 20 per cent, although some are alive with arrested disease; the natural life history of some thyroid carcinomas spans decades.

A case of thyroid carcinoma in a 9-year old child is reported.

Analysis does not show any remarkable difference in the clinical manifestations, histologic types or progress of the disease between adults and children.

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SURGICAL TRANSPLANTATION OF TUMOR CELLS

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For the past 6 decades the transplantation of tumor cells in surgical wounds has been reported from time to time. A great deal has been written about the cause and prevention of this unfortunate occurrence. In talking to various surgeons I have found that many of them are not cognizant of this very real possibility; some, even though they know transplantation occurs, seem to think the occurrence is rare.

I have attempted to limit this review to human tumor cells; however, occasional mention is made of the outstanding work being done in the research laboratory. Experiments, such as those of Greene[21], produced important new information toward our knowledge of cancer growth.

The members of our tumor clinic believe that the occurrence of transplant in operative wounds is common and if proper precautions are taken the incidence can be markedly reduced. Most of the precautions which we use are mentioned in the literature and are standardized procedures in many clinics.

The one fact which is repeatedly emphasized in the literature is that implantation may occur from practically any type of cancer, located in almost every section of the body.

In 1891[18] successful tumor transplantations from a malignant tumor of one breast to the other breast was reported. The very words of Halsted[25] make one realize that the spread of tumor cells was known prior to 1900—"Tumors should never be harpooned, nor should pieces ever be excised from malignant tumors for diagnostic purposes. Breast tumors should not be excised on the operating table prior to their removal".

Between 1900 and 1910 Lawrie[31] stated, "Where the original tumor has been removed entire inside a mass of surrounding tissue, like a core of paper in a ball of worsted, there will be no possibility of transplantation, but when the tumor is broken into during an operation the risk of transplantation must be great. In such a case, small portions conveyed by the fingers or knife might easily find a suitable position on the raw surface for renewed growth, hence the so-called recurrence". Ryall[40] pointed out that contamination of the instruments used in the operation with cells removed during the operative procedure was a frequent cause of recurrence. Numerous examples were cited in which cancer of the breast, tongue, lip, larynx, rectum and colon were implanted at operative sites through cancer infection of the wounds by contaminated knives and needles. In 1908, Ryall[41] recommended a complete change of gloves, drapes, instruments and re-preparation of the operative site after biopsy of a malignant tumor had been completed and the exploratory incision closed. Butlin[9] also recommended that

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TABLE I

Transplants* are known to occur from tumors of the following organs:

Skin	Uterus
Thyroid	Ovary
Salivary glands	Prostate
Parathyroid	Testicle
Lung	Bladder
Breast	Kidney
Esophagus	Bone—including benign giant cell tumor
Stomach	Lymph nodes—including various sarcomas
Colon	

* The tumor cells may be transplanted to the operative wound, skin donor sites or, at times, to epithelial or serous membranes.

the instruments which were used for the purpose of diagnosing malignant tumors must not be used again until they had been boiled. Bland-Sutton[4] was of the opinion that one of the most vital principles of surgery in malignant disease is that cutting into cancerous tissue leads to a spread of the disease. Hubbard[29] in 1909 reported transplantation of squamous carcinoma of the skin to the area of skin graft.

Between 1910 and 1920 W. J. Mayo[36] reported a case of implantation of a cancer into a left rectus colostomy wound. Bainbridge[2] and Greenough[22] wrote about cutting into cancerous tissue and spreading the disease. They gained their views by following up the individual patients rather than by the actual finding of tumor cells on the knife.

In the literature from 1920 to 1930 Primrose[18] recorded a case of an ovarian malignancy in which ascitic fluid was aspirated and subsequently injected in the submammary region as an experimental therapeutic procedure; a malignant tumor appeared in the breast and axillary glands. The perilous effect of tumor cells adherent to the blade of the knife is clearly brought out by Bloodgood's[5] statement which stressed the danger in excising a cancer of the breast without the use of the cautery and then waiting longer than 2 weeks before the radical operation.

Between 1930 and 1940 Dvorak[16] reported a case of local recurrence within the abdominal wall 13 years after operation on an ovarian neoplasm. In 1933 Ewing[17] recommended the change of gloves and instruments after the performance of a biopsy of malignant tumors. Hellwig[23], in 1932, spoke of stimulation of growth and dissemination of tumor cells through the blood and lymph vessels. He thought that these sequelae could be explained by the dropping of viable tumor cells which actually were transferred into the blood vessels or tissues by the dissecting knife. Also, in 1932, Szymonowicz[43] reported a case of implantation of renal hypernephroid tumor with secondary tumors in the bladder and urethra.

In 1936 Saphir[42] stated that many surgeons were discarding the knife after it had been used for the removal of a biopsy of a malignant tumor and continuing the radical operation with another knife or with a second set of instruments. This practice, however, was not universal and the same instruments were still used by some men for both the removal of the biopsy specimen and for the radical operation. This communication was the result of examination of material which adheres to the blades of knives used for obtaining biopsies of tumors, particularly breast tumors. All the knives with which various types of malignant tumors were incised, were examined shortly after they had been used. Either direct smears were made from the respective blades or the blades were washed with a small quantity of saline and smears were made from this suspension. Invariably, smears which were made from the material on the knives used to cut through the tumor showed neoplastic cells. In some instances the malignant cells were so abundant that at low magnification their numbers were comparable to that of the erythrocytes on a blood smear of average thickness. Also, smears which were made from material on the knives used for removal of the primary tumor for biopsy before the radical breast operation was performed revealed tumor cells Martin and Ellis[35], in 1934, described a method of staining with hematoxylin-eosin in their studies of aspiration biopsies. Hickling[2] had, in 1931, described a method of supravital staining to prove viability of cells.

From 1940 to 1950 Greene[21] reported that viable tumor cells had been transferred from one species to another and successfully transplanted. White[39], in 1943, reported a series of 254 cases from the Roosevelt Hospital, New York, in which the recurrences were stated to be "due to the fact that the carcinoma is already widespread (lymphatic emboli) and beyond the reach of surgery". Brown[7] presented evidence that a tumor recurring in the skin after an operation for radical removal of the breast for carcinoma is a recurrence in the skin itself and not a generalized chest wall metastasis. These fall into two categories. First, the tumor should involve only the skin itself with perhaps only a small amount of subcutaneous tissue. If there is any involvement of the deeper tissues such as deep fascia or the tissue of the chest wall this makes it likely that the skin involvement is of deeper origin. Second, the tumor should be histologically not only a type of tumor that does not primarily involve the skin, but also a type that does occur in the breast and closely approximates the original tumor for which the primary operation was performed. Brown reported 3 cases, all of which, he believes, were caused by implantation. Rodman, as cited by Brown[7], reported 132 cases with 3 recurrences (2.2 per cent) in skin. He believes the low rate of recurrence is the result of a wide removal of fascia. It is Brown's belief that the important part of the operation is the careful undercutting of the skin to the limits of deep removal.

Brandes and White[6], in 1946, reported two instances of tumor growth at the site of paracentesis or thoracentesis wounds in carcinomatosis of the peritoneum or pleura. They also gave an excellent case presentation of transplantation of a highly malignant carcinoma of the breast from the mastectomy site to a skin donor area on the left thigh. They discount the possibility of metastatic transfer

by way of blood or lymph stream because of the distance. This is an obvious case of implantation but I would like to mention one of our recent patients with adenocarcinoma of the breast. Mastectomy was performed elsewhere and she had been followed in our tumor clinic for 2 years. One week prior to death a nodule was noted in the thigh and this was removed. This was reported as metastatic adenocarcinoma. Postmortem examination 1 week later demonstrated extensive pleural metastasis but no other primary lesion was noted. This patient did not have a skin graft. Brandes and associates[6] reported that they had centrifuged the contents of wash basins used during cancer surgery and had found well preserved tumor cells in the sediment. They stated that when normal saline solution was used the cells apparently remained viable for longer periods.

In 1946 the work of Hovenanian and Deming[27] on transplantation of urinary bladder tumors to the anterior chamber of the guinea pig's eye is of interest in showing the possibilities of uro-epithelial neoplastic transplants. In 1947 Lumb[33] presented a case of transplantation of transitional cell carcinoma of the bladder. At the secondary procedure, 6 weeks after the first suprapubic operation, tumor was found in the abdominal scar. Deming[15] has stated that some urinary bladder tumors are capable of heterologous transplantation while most are not. Previously 4 were transplanted successfully and then he had 127 consecutive failures. In 1950 Franksson[19] presented 4 cases of bladder carcinoma which were transplanted into the surgical wound. Weiss and Bonner[44] reported the first case in American literature of transplantation of urinary bladder carcinoma into the surgical wound.

Macalpine[34], in 1948, reported the occurrence of implants in the ureter arising from adenocarcinoma of the renal parenchyma and in reviewing the literature collected 12 cases, the majority of which occurred following surgical removal of the primary renal tumor. Hovenanian[26] and Howell[28] both reported a case of implantation of renal parenchymal carcinoma into the ureter. Leadbetter[32] suggested that better exposure of renal tumors through an adequate approach, reduces the amount of manipulation necessary for removal of the kidney, and thereby decreases the possibility of transplantation of neoplastic cells. In 1947 Burke[8] presented a case report of a patient who had a parathyroid adenoma. At operation a fragment of the adenoma was transplanted between the strap muscles of the neck. Two years later the patient returned with a recurrence of all manifestations of hyperparathyroidism and a recurrent adenoma at the site of the graft. Pathologically, neither tumor was considered malignant. In 1948 Joynt[30] presented a case to illustrate the operative transplantation of benign giant cell tumor of bone to a distant soft tissue site. The primary tumor originated in the upper end of the tibia and the local recurrence 9 months later showed a typical benign histologic picture. The transplantation occurred in the soft tissue in the left iliac region at the site where bone graft was obtained at the time of the original operation on the tibia. Black[3], in 1950, mentioned a case of implantation of a parathyroid cancer into the soft tissue where it grew and finally caused the death of the patient. Goligher, Dukes and Bussey[20] analyzed the cases of 23 patients with suture line recurrences after anterior resection of the rectum. They con-

cluded that, in at least half of these 23 patients, the recurrence was not caused by incomplete resection of intramurally spread tumor but rather to the implantation of viable cancer cells upon the raw surfaces of colon presenting at the anastomosis. That this phenomenon is not peculiar to anterior resection, but occurs in resections elsewhere in the colon, was demonstrated in 2 additional patients. One had a resection of the splenic flexure and the other a colectomy and ileosigmoidostomy. In 1951 Cole[11] stated he was "deeply concerned over the possibility that we may be negligent in the prevention of the relatively frequent recurrences of tumor at the stoma when anterior resection for carcinoma of the rectum and rectosigmoid is concerned. Yet when we cut across the lumen of the bowel distal to the lesion we do little or nothing to prevent transplantation of these desquamated cells from the lumen into the cut section of the bowel at the anastomotic site". In 1953 Clark, Leadbetter and Campbell[10] reported 1 case of implantation of cancer of the prostate into the abdominal wound following total prostato-vesiculectomy and total cystectomy. Another prostatic cancer was transplanted to the subcutaneous tissue of the perineum by needle biopsy. McGrew, Laws and Cole[37], in 1954, stated that, if implantation of malignant cells does occur during anterior resection of the colon, it probably is produced by contamination of the suture through contact with the uncleansed mucosa, with implantation of cells into the wall of the intestine as the suture is passed through it. There is, of course, the possibility that implantation of malignant cells may take place as

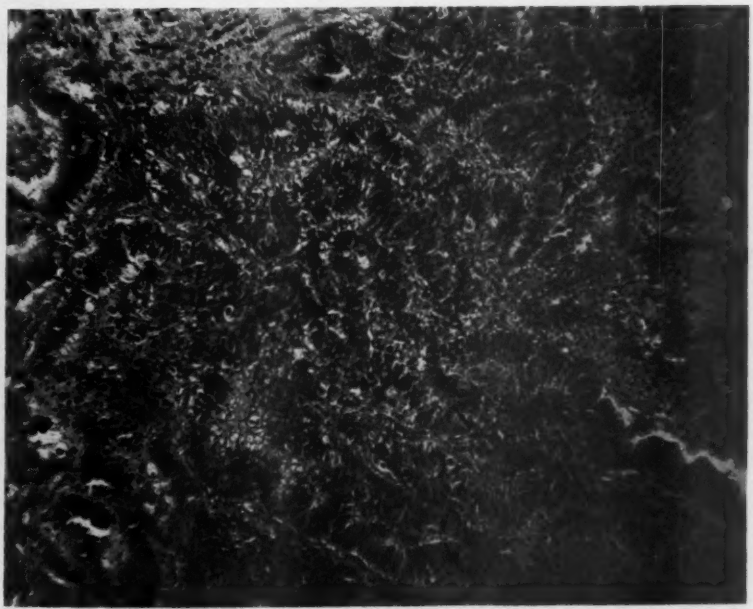

FIG. 1. Case 60277. Photomicrograph of original lesions of the stomach showing adenocarcinoma. 70× magnification H & E stain.

the bowel segment is excised, the cells coming in contact with the raw cut surface of the bowel. They took smears, processed by the method of Papanicolaou and carefully looked for malignant-appearing cells. A high percentage of the patients had free tumor cells in the lumen of the colon.

In March 1955 Ackerman and Wheat[1] presented one of the best reviews of this subject which has appeared in American literature. They presented many new case reports which aid in making the picture of transplantation more complete. Needle biopsy is mentioned as a method of transplantation of tumor cells. In 1 case, melanoma which grew along the tract is mentioned. Skin graft implantations are mentioned, such as the plasma cell tumor of the chest wall which was implanted on the donor site of the leg. Frantz, as cited by Ackerman[1], reported 2 instances of local recurrent papillary carcinoma of the thyroid following an incisional biopsy. Ackerman reported several subcutaneous implants of tumor cells: (1) Seven years following enucleation of a supposed benign thyroid tumor; (2) Implantation of a chondrosarcoma of the femur is mentioned; (3) Chest wall implantation in 2 patients with peripheral lung tumor which was broken into at the time of surgery is mentioned; (4) Another patient with carcinoma of the stomach had implantation into the abdominal wall scar. This implantation was removed and the patient was well 5 years following this procedure; (5) Still another patient with papillary adenoma of the rectosigmoid had implantation into subcutaneous tissue in a surgical scar. This recurrence was resected. One

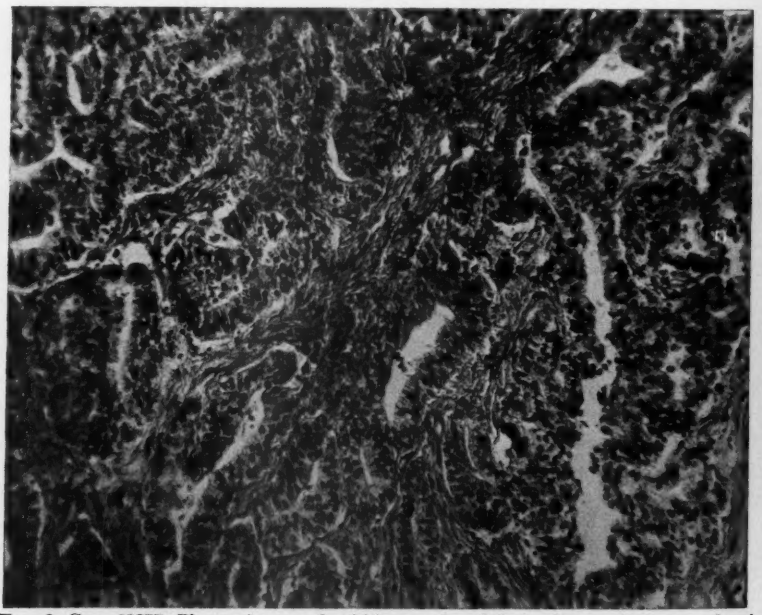

FIG. 2. Case 60277. Photomicrograph of biopsy of nodule in the surgical scar, showing comparable microscopic pattern of lesion. 70× magnification H & E stain.

patient with carcinoma of the endometrium had the uterus torn into at surgery. Eighteen months later an extramucosal mass in the rectosigmoid area was resected by the abdomino-perineal approach, resecting a well-defined tumor nodule in the wall. Regional nodes revealed no evidence of tumor and microscopic sections of both tumors were identical.

Crile[14], in July 1955, posed the question: "Is biopsy safe"? He stated that there was increasing evidence that operations which do not completely encompass cancer but cut across it may spread cancer and accelerate the course of the disease. A case was mentioned of papillary carcinoma of the thyroid which was diagnosed by needle biopsy and removed surgically 2 days later. It recurred after 2 years as a skin nodule at the site of the needle puncture. Four years after the biopsy the patient died of systemic metastases. He stated that biopsy is useful in diagnosis and safe if employed carefully and in selected cases. If used indiscriminately, he stated, it may spread disease and shorten life. He advances the philosophy that in patients with incurable cancer the surgeon has a grave responsibility; operations, when they can do no good, at least should do no harm. In August 1955 Pomeranz and Garlock[38] presented cases where viable malignant cells could be rubbed off the serosal aspect of colonic neoplasms during operative manipulation. They reported 20 unselected cases where smears were taken from the serosal aspect of the colonic tumor as soon as the peritoneal cavity was

FIG. 3. Case 60277. Photomicrograph of tumor in abdominal wall, proving implantation into the surgical scar. Note changed histopathologic pattern of adenocarcinoma. 70× magnification H & E stain.

entered and before any manipulation of the tumor was carried out. Papanicolaou technic was used to prepare the slides and careful studies for tumor cells showed unmistakable carcinoma cells in 2 patients (10 per cent). They advocated the use of a "colon cover" and the use of occlusive ligatures as recommended by McGrew and his associates[37]. The colon covers that they used were modified abdominal pads. In September 1955 Cole[13] mentioned that their original reported incidence of 10.9 per cent[12] recurrence in the suture line following resection of the colon in 55 patients had remained approximately the same, being 9.9 per cent in 140 patients. They recommended preliminary ligation of the bowel with umbilical tape above and below the tumor. After the involved segment

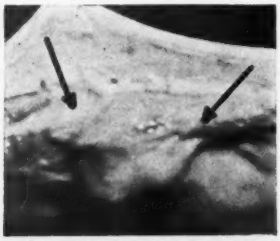

FIG. 4. Case 63478. Gross photograph (at autopsy) showing implantation into abdominal surgical scar.

FIG. 5. Case 63478. Photomicrograph of lesion in figure 4, showing adenocarcinoma in abdominal wall. 70× magnification H & E stain.

was removed the open ends of the bowel to be anastomosed were irrigated to remove stray cells desquamated or dislodged from the tumor.

The following cases of ours illustrate transplantation of tumor cells. I believe that every surgeon has or will, at some time in his career, transplant tumor cells.

CASE REPORTS

The first patient, case 60277, Mr. A. P. an 84 year old white man had a palliative subtotal gastrectomy because of carcinoma of the stomach. Ten weeks postoperatively a nodule was noted in the surgical scar and biopsy revealed carcinoma which microscopically resembled the primary lesion from the stomach. Autopsy was performed 10 months after the original surgery and implantation was then proved. There was no connection with the intra-abdominal tumor mass.

The second patient, case 4404, Miss R. M. a 70 year old white virgin, was seen initially with the chief complaint of vaginal bleeding. This bleeding was of 12 weeks duration. Dilatation and curettage was performed at which time the hymenal ring was torn. Six months later 3 small masses were noted in the hymenal ring. Pathology report revealed implants from endometrial carcinoma.

Another patient, case 11948, Mrs. M. W., had a bronchogenic carcinoma. Pneumonectomy was done elsewhere. At the time of death she had proved implants in the surgical scar on the chest wall.

A fourth patient, case 28768, Mr. J. G., had carcinoma of the ascending colon. The original surgery was a right hemicolectomy and tumor cells were transplanted into the suture line of the bowel. This lesion was later excised and an end to end anastomosis performed. The patient is living and well 5 years later.

The last case, 63478, Mr. J. W. a 38 year old white man, had an exploratory laparotomy with the intention of doing an abdomino-perineal resection for carcinoma of the rectum. The disease was far advanced and since the rectum was nearly obstructed from carcinoma a palliative transverse loop colostomy was performed. A biopsy was taken from the mesentery. Four months later at postmortem examination an obvious transplant was found in the exploratory incision scar outside of the peritoneum.

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THE EFFECT OF THERMAL TRAUMA ON ANTIBODY FORMATION IN RABBITS*

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Infection in the burned patient always has been a perplexing problem. In studying this problem attention usually has been focused on the burned area and its local care because infections are more readily apparent at the local site. An increased number of deaths in burned patients attributed to septicemia have been reported recently. However, the cause of this complication and the best methods of its treatment are uncertain. Among patients sustaining severe burns it is believed that many now are surviving because of fluid and electrolyte imbalance who would have died a few years ago. The primary cause of death in such patients is septicemia. It probably is true that the eschar provides the focus of infection.

It was decided to determine whether or not thermal trauma altered the antibody response, thus making the body less resistant either to local or systemic infection. I^{131}-labeled bovine gamma globulin was used by Dixon and associates[1] to show the nonimmune and immune response in rabbits. This was the labeled antigen used in this experiment.

METHOD

I^{131} with a half-life of 8 days has an advantage in that it can be attached to protein in traceable amounts without measurably altering the immunologic specificity. It also remains attached to the protein as long as the latter is immunologically detectable. Furthermore, when the iodine is liberated by protein metabolism, it is not incorporated by synthesis or interchange in appreciable amounts into the rabbit's own proteins as determined by activity measurements of plasma protein fractions after the administration of I^{131}-labeled homologous globulin.[2]

Seventeen white rabbits (3–4 kg. weight) were used in this experiment; 6 were used as controls, while the remaining 11 rabbits were subjected to thermal injury. All of the animals were fed potassium iodide daily for 1 week prior to the experiment in order to saturate the thyroid gland with iodine. There was little or no possibility of the thyroid gland interfering with the rate of disappearance of the iodinated bovine gamma globulin. Once the iodine was liberated from the antigen, however, it was thought that it would be better to have the iodine excreted rapidly by the kidneys rather than to have it picked up by the thyroid gland and released at a later date.

The animals were anesthetized with intramuscular injections of paraldehyde,

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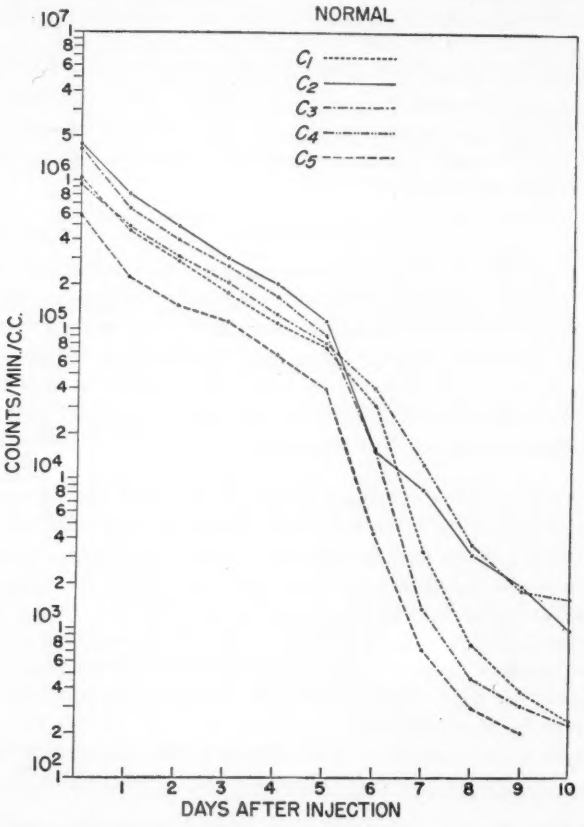
following which 11 of the 17 rabbits were subjected to a 15–20 per cent body surface burn by immersing the back of the animal in 90 C. water for 20 seconds. One to 10 mg. (100–300 microcuries) of iodinated bovine gamma globulin was injected into the femoral vein which had been exposed by a small cut-down. Fifteen minutes after the antigen had been injected, a blood sample was taken via cardiac puncture. Blood samples were taken from a marginal ear vein every 24 hours for 9 days.

The rabbit blood was centrifuged and 2 cc. of plasma was placed in a counting tube and the radioactivity was measured in a thallium-activated, sodium iodide scintillation-cup counter. Since the radioactivity of the earlier blood samples was too great to count accurately, these were set aside in a refrigeration unit and allowed to lose some of their radioactivity by decay until the counting rates were less than 40,000 counts per minute. All of the samples had counting rates of more than 3 times background; correction was made for coincidence. Correction factors



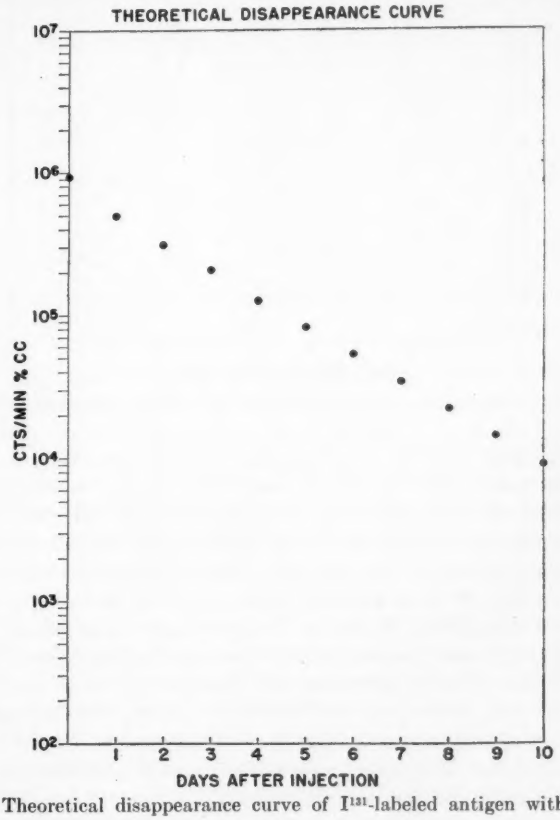
GRAPH 1. Disappearance curves of I^{131}-labeled antigen in 5 normal rabbits.

also were applied for purposes of comparison, hence all specimens were counted at the same time, *i.e.*, at the time of injection of the antigen.

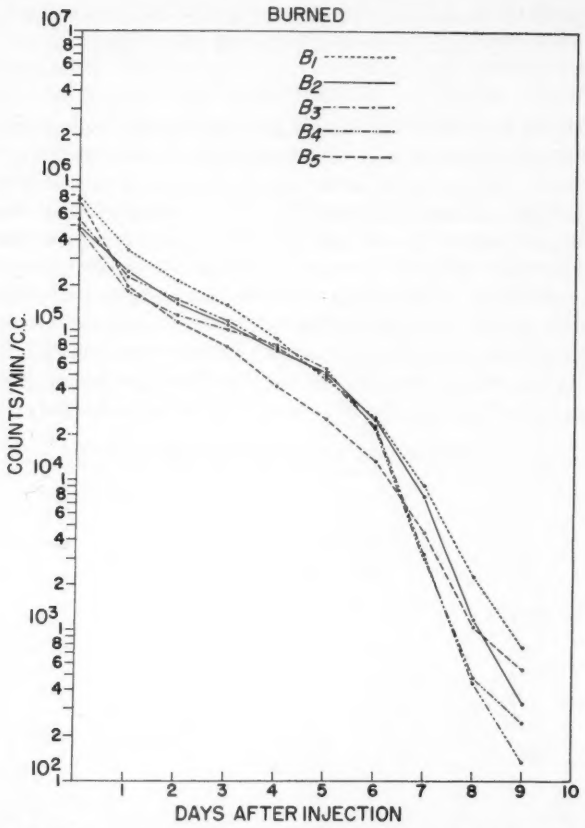
RESULTS

The disappearance rates of the bovine gamma globulin in 5 of the unburned control rabbits had a configuration similar to that shown in graph 1. Variations in both the size of the injectate and the size of the animals provided some difference in the actual counting rates, but the rates of disappearance were similar. The disappearance rate of the antigen was very rapid during the first 24 hours and resulted not only from the normal loss of the bovine gamma globulin but also from the diffusion of the antigen into the extracellular compartment.[3]

Following the first 24 to 36 hours, the rate of disappearance slowed markedly and revealed a normal nonsensitized disappearance rate of bovine gamma globulin in the body of the rabbit. Starting on the fifth day, the rate of disappearance increased markedly. This is believed to be associated with the body's production



GRAPH 2. Theoretical disappearance curve of I^{131}-labeled antigen without antibody response.



GRAPH 3. Disappearance curves of I^{131}-labeled antigen in 5 burned rabbits.

of antibodies in response to the antigen. This new rate was so rapid that, by the ninth day, the radioactivity of the plasma was barely above background count.

If no antibody response occurred, the investigator would expect to find the disappearance rate to continue as a linear function as illustrated in graph 2.

Graph 3 is a plot similar to graph 1; it shows the disappearance rates of the tracer-tagged antigen in the plasma of 5 of the burned animals. The disappearance rate was almost identical with that of the control group (graph 1). The initial, rapid disappearance rate was seen along with a much slower disappearance rate for the next 5 days. The disappearance rate from the second to the fifth day was almost linear when plotted on semilogarithmic paper. Beginning on the fifth day, the rate of disappearance increased markedly and within 3 days virtually all of the radioactive antigen had disappeared from the circulation.

Rate constants determined in both the control and burned animals are shown in the table. R_1 is the rate constant determined by using the radioactive levels of

Summary of rabbit data
Burned & control animals with bovine gamma globulin

Animal	Rate Constants			Day of Initial Antibody Response	Bovine Gamma Globulin	
	$R_1(a)$	$R_2(b)$	$R_3(c)$		Mgm. I^{131}	JUC I^{131}
Burned Rabbits						
B-1	0.447	1.260	0.813	5.8	3.6	184
B-2	0.383	1.732	1.349	6.1	3.6	184
B-3	0.224	1.98	1.756	5.5	10.8	93
B-4	0.374	1.98	1.606	5.7	10.8	93
B-5	0.521	1.215	0.694	5.8	6.85	109
B-6	0.379	2.038	1.659	5.4	2.7	196
B-7	0.359	1.194	0.835	6.6	2.7	196
B-8	0.347	1.823	1.476	6.6	2.7	110
B-9	0.485	1.194	0.709	4.2	1.3	110
B-10	0.431	1.733	1.302	7.2	1.3	93
B-11	0.295	1.98	1.685	4.8	10.8	
Mean	0.386	1.555	1.169	5.8		
Control Rabbits						
C-1	0.347	2.10	1.753	5.8		200
C-2	0.347	1.26	0.913	4.8		200
C-3	0.347	2.31	1.963	5.2		200
C-4	0.347	1.24	0.893	5.7		200
C-5	0.352	2.038	1.686	4.8	6.85	109
C-6	0.430	2.566	2.136	5.7	6.85	109
Mean	0.362	1.918	1.556	5.4		

Notes: (*a*) R_1 = First exponential removal phase. (*b*) R_2 = Second exponential removal phase. (*c*) R_3 = R_1 Minus R_2.

the second, third and fourth days. R_2 is the rate constant of the second exponential removal phase starting on the fifth day and continuing through the eighth or ninth day. R_3 is the result of subtracting R_1 from R_2.

R_1 is virtually a linear function resulting from the normal process of elimination of this foreign protein which started on the second day and continued through the fifth day; this disappearance rate occurred prior to antibody formation. This rate was found to be relatively constant from animal to animal, regardless of the size of the animal or the amount of injectate (*see* table). The mean slope (R_1) for the control rabbits was 0.362 and the mean for the burned rabbits was 0.386. The mean slope of the second exponential rate (R_2) was 1.918 in the control group and 1.169 in the burned group. By subtracting the first exponential rate from the second exponential removal rate, the third rate (R_3) was obtained.

Insofar as the R_1 was similar in both burned and controlled groups and was the result of a normal nonimmune excretory process, it was thought that, by subtracting this calculated disappearance rate from the second exponential phase, the actual removal rate due to antibody formation would be shown. The

mean resultant rate (R_3) for the control rabbits was 1.556, for the burned rabbits 1.169. A "t" test of the means of R_3 was performed in order to compare the control group and the burned group. Our data showed a "t" value of 1.46, whereas $t_{0.5}$ should be 2.13 in order to show a statistically significant difference.

The point of change from the first exponential removal phase to the second exponential removal phase was determined by extending the lines of both slopes of the first and second exponential phases until they intersected; that point was taken as the critical time when the antigen removal rate began to change. It is true that there might have been a short period of increased disappearance rate prior to the point of selection, but more frequent blood samples were not taken to make an accurate determination of this point because of the possibility of introducing the factor of acute blood loss into this experiment. As can be seen from the table, the mean time of change for the control rabbit group was 5.4 days, for the burned rabbit group 5.8 days.

DISCUSSION

Available evidence indicates that protein-bound I^{131} is a stable chemical link which, *in vitro*, resists wide changes in temperature, pH, salt exchange dialysis, prolonged storage and enzymatic action. *In vivo*, it appears that the iodine remains attached to the protein as long as the latter is immunologically detectable.[2]

Insofar as I^{131}-labeled bovine gamma globulin is handled in much the same way as normal globulin in the rabbit prior to antibody production, it should be expected that the first 24 to 36 hours would demonstrate the process of the diffusion of the proteins into the extracellular compartment in addition to the normal excretory rate. On or about the fifth day, antibody formation increases the rate of antigen disappearance. By checking the disappearance rates, it was thought that it would be possible to determine whether or not antibody formation was inhibited by thermal injury. In this experiment, we were unable to demonstrate any difference between the burned and unburned animals in the manner in which the bovine antigen was handled.

Clinically, septicemia does not appear to be a problem in the less severely burned individuals. Consequently, the extent of the burn may influence the antibody formation rate. An attempt was made to increase the amount of body surface area burned in the rabbit, but this was attended with a very high mortality rate. It was thought inadvisable to institute fluid therapy in these more severely burned animals for fear that this might introduce another variable. Consequently, the most severe injury was a 20 per cent third degree burn over the dorsal surface of the rabbit's body.

SUMMARY

Iodinated bovine gamma globulin was injected into normal and burned rabbits. The rate of disappearance of this labeled antigen was determined.

There was neither change of rate of removal in any of the phases of the antigen disappearance curve nor any apparent delay in actual antibody formation itself between the control animals and those with a third degree burn covering 20 per cent or less of the body surface.

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REPAIR OF DIFFICULT HERNIAS BY THE USE OF FULL-THICKNESS SKIN GRAFT*

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The repair of a major hernial defect of the abdominal wall can prove to be both time consuming and difficult. Occasionally there is inadequate tissue to effect a satisfactory closure and it becomes necessary to reinforce the area. For this purpose, many materials have been used, among which are fascia lata, tantalum wire mesh, polythene, cutis, and full-thickness skin grafts. Of the autogenous materials (fascia lata, cutis, and skin graft) fascia lata is most commonly used in this country. Authors in European and South American countries, have reported extensive use of cutis and full-thickness skin grafts. The implanting of skin for repairing hernias was reported by Loewe in 1913. Many reports, although favorable, nevertheless reported failures and such complications as cyst formations.

In my own practice, the occasion has arisen whereby extra material was needed to effect an acceptable hernia repair. Full-thickness skin has served this need effectively and without complication.

Technic for Repair of Inguinal Hernia with Skin Graft

Meticulous skin preparation of both the operative and donor site should be emphasized. It is not believed necessary to use special advanced preparation of the skin. The usual shaving and generous scrubbing with alcohol, ether and merthiolate suffices.

The incision is planned so as to remove an elliptical piece of skin at the operative site which may be used as a graft. Where the hernia is large with redundant skin, this is accomplished easily. Where the skin at the site of the incision is not of suitable quality to use in the repair, the defect is exposed and its size determined. A suitable graft then is taken from another site and placed in aqueous merthiolate solution until needed. Flaps of the external oblique aponeurosis are developed, especially superiorly to allow subsequent placement of the graft. The hernial sac is treated as in any other type of repair.

In recurrent, direct, and indirect hernias where there is considerable weakness of Hesselbach's triangle, we use the McVay type of repair, suturing the transversalis fascia and conjoined tendon to Cooper's ligament. In children and young adults who usually have indirect hernias, we use the Bassini type repair, suturing the conjoined tendon to the inguinal ligament. In both types of repair we free the spermatic cord of excessive tissue, leaving the vessels, the vas deferens nerve and a small amount of adherent muscle and connective tissue. The transversalis

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FIG. 1. Illustration showing how cord structures are brought out through a tunnel made by the overlapping of the aponeuroses of the external oblique muscle. The opening in the inferior flap through which the cord passes should not be directly over the internal inguinal ring.

fascia then is buttressed about the cord, thus snugly tightening the internal ring. Where the tissue is weak and needs reinforcing, the conjoined tendon is sutured to Cooper's ligament medially and then to the inguinal ligament laterally. When this is completed the graft is removed from the merthiolate solution and carefully cleansed of all adipose tissue. It is cut to the size desired and sutured to the anterior rectus sheath, the fascia over the pubis, the inguinal ligament and to the internal oblique muscle. The graft is split to allow passage of the cord structures. It is fixed about the internal ring. It is of utmost importance to see that the graft is sutured under tension. Eisele and Starkloff recommend placing sutures through its midportion to obliterate any dead space. I have not found this necessary. The cord usually is not transplanted superficial to the external oblique aponeuroses (fig. 1). Where the cord is transplanted superficial to the external oblique fascia, I have found an unduly high incidence of recurrence at the site of the internal ring (Halsted's operation).

Where the defect is only moderate, we have reinforced the area by using a strip of skin rather than a patch. It is inserted as a suture similar to strips of fascia lata, or fascia obtained from the external oblique aponeurosis as in the McArthur technic (fig. 2). Gentleness, asepsis, and meticulous hemostasis are paramount to a successful repair.

Technic Used in the Repair of Incisional Hernias

The method described by Cattell has proved quite satisfactory in managing most incisional hernias. It has proved superior to the layer dissection method.

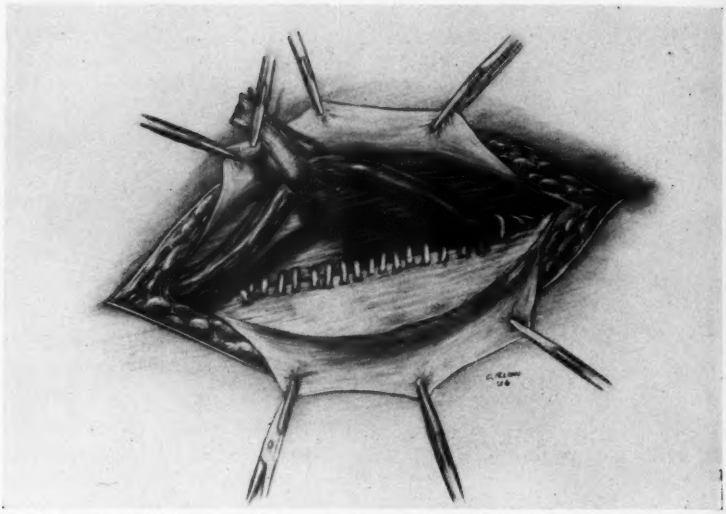

FIG. 2. Repair of left inguinal hernia using strip of full-thickness skin to reinforce hernial defect. Note that strip passes around internal ring so as to reinforce it but not constrict the cord.

An elliptical piece of skin over the hernia is excised, leaving sufficient skin to allow approximation of the edges without tension. This excised skin is saved as it may be used in the subsequent repair. The dissection is carried down to the fascia. The hernial sac which usually is subcutaneous is opened and the contents freed and reduced. The neck of the sac with its firm fibrous borders is identified. A running suture of no. 1 chromic catgut is placed through the fibrous tissue to close the neck of the hernia. Care is taken to place this near the innermost border of the neck. After this closure, an incision is made 2 cm. from the suture line. This incision is carried entirely around the neck of the sac and is made parallel to the anterior abdominal wall. It is carried through the adherent fibrous tissue of the sac, thus developing a firm fibrous layer to suture together (figs. 3 and 4). These edges then are approximated over the first suture line with interrupted sutures thus completing a second layer of closure. In accomplishing the above, you usually will expose muscle tissue. This is freed over the entire circumference of the hernia and approximated loosely with interrupted sutures, thus making a third layer of closure. The muscle planes adjacent to the hernia usually demonstrate some fibrosis and constitute fairly strong tissue. By lifting up on the inner border of the divided sac and dissecting it free, one can readily develop the external fascial layer and approximate this layer, thus making the fourth layer of closure. This outer layer of fascia may be deficient and it is here that the skin graft most often proves helpful. The skin previously obtained now is cut to size, freed of all fat, and sutured in the defect under tension by means of interrupted silk sutures. The subcutaneous fascia and skin are approximated without drainage (fig. 5).

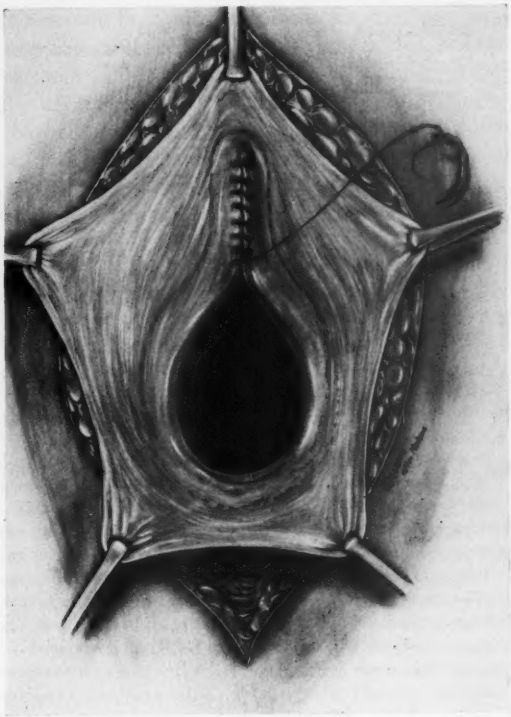

FIG. 3. Illustration showing Cattell's method of repairing an incisional hernia. Running catgut suture through the neck of the sac forms first layer of closure. Dotted line shows where incision will be made to develop a flap for second layer of closure.

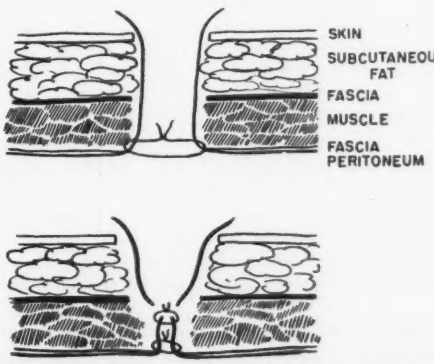

FIG. 4. Cross sectional illustration of repair of incisional hernia. Upper drawing shows suture through neck of sac before it is pulled tight. Note that it catches peritoneum and fascia which usually is fused at this point. Lower drawing shows sac sectioned as marked in figure 3 and sutured with interrupted silk or cotton.

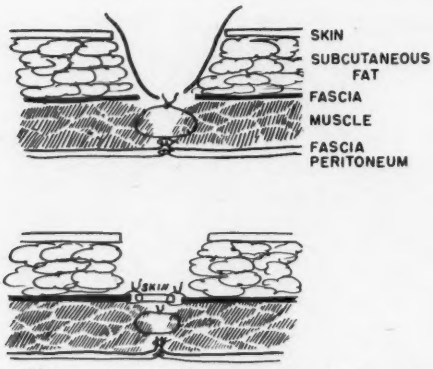

FIG. 5. Cross sectional illustration of closure of muscle layer and in lower drawing showing full-thickness skin graft being used to bridge defect in anterior fascial sheath.

TABLE 1

Comparison of infection using skin and other methods of herniorrhaphy

Skin		Other Material	
Mair (1946)	3.3%	Burdick (1937) Fascia	4.7%
Marsden (1948)	6.1%	Shelly (1940) Conventional	3.5%
Zavaleta (1950)	2.36%	Maingot (1940) Floss Silk	2.0%
Strahan (1951)	4.3%	Thompson (1951) Polythene	3.2%
Eisele (1951)	0.0%	Palumbo (1954) Conventional	2.0%

TABLE 2

Comparison of recurrences using skin and other methods of herniorrhaphy

	Cases	Recurrent	Per Cent
Zavaleta (Skin)	211	3	1.4
Eisele (Skin)	17	1	5.8
Strahan (Skin)	369	25	6.8
Ali (Skin)	104	1	1.0
Burdick (Fascia)	975	282	29.0
Maingot (Floss Silk)	1000	30	3.0
Barnell (Tantalum)	47	1	2.0
Conventional			
Indirect	—	—	6.1
Direct	—	—	19.0

COMMENTS

Whenever skin is used to reinforce a hernia repair, one must use meticulous surgical technic, using careful sharp dissection which minimizes trauma and reduces the amount of devitalized tissue. Hemostasis and asepsis must be excellent. The graft must be of good, healthy, elastic skin and free of any fat or subcutaneous tissue. It must be sutured in place under tension, being careful not to

leave dead space above or below it. Antibiotics are used routinely, usually penicillin and streptomycin along with erythromycin. All patients on whom skin is grafted will show more than the usual amount of induration and reaction. This usually subsides in about 2 weeks. The incidence of suppuration or drainage is no more frequent than a conventional surgical repair (table 1). Although we have not had the opportunity of reopening one of these hernias, it is reported that the epithelial elements in general disappear and the fibro-elastic elements remain as a strong supporting structure. The instance of recurrence is low (table 2).

CASE REPORTS

Case 1. Mrs. M. B., aged 63, in 1951 developed symptoms of diabetic mellitus and cholecystitis for which a cholecystectomy was done. This was complicated by a pulmonary infarct with a pleural effusion. Postoperative wound infection culminated in a large incisional hernia.

In June 1952, the incisional hernia was repaired using a full-thickness skin graft as a substitute for the deficient anterior rectus sheath. On the second and third postoperative days, she had a fever of 101 F. which subsided to normal by the eighth postoperative day. She was given penicillin and streptomycin for 1 week. There has been no evidence of recurrence 3½ years later.

Case 2. Mr. J. B., aged 37, had a right inguinal hernia repaired 4 years previously. He now is hospitalized for repair of a large left inguinal hernia. At operation a large direct inguinal defect was encountered. The sac was freed, the contents reduced and closed with interrupted silk sutures. Following removal of the hernial sac, the cord was freed of excessive fatty tissue and the internal ring narrowed by suturing the transversalis fascia snugly about it. The transversalis fascia and conjoined tendon were sutured to Cooper's ligament with interrupted silk sutures. Because the tissue was of poor quality it was thought that additional reinforcement was necessary and an elliptical piece of skin was obtained from the site of the incision and utilized as a full-thickness graft. The cord was transplanted between the overlapping leaf of the external oblique aponeuroses. Postoperatively the patient was given penicillin and streptomycin and left the hospital on his fifth postoperative day. Sutures were removed at the office on the seventh postoperative day and it was noted at that time he had the usual increased induration but otherwise he had an uneventful recovery from his surgery. His hernia is still holding satisfactorily 2½ years later.

Case 3. Mr. A. J., aged 69, had a bilateral inguinal herniorrhaphy in 1950. Approximately 4½ years later, while doing heavy lifting, he noted a recurrence of his hernia on the right side. Physical examination showed a man in good physical condition for his age with a recurrent right direct inguinal hernia.

At operation it was noted that he had had a Halsted type repair at the previous operation with a recurrence at the internal inguinal ring. The hernia sac was removed, the cord freed of fat and extraneous tissue and the internal inguinal ring narrowed by suturing the transversalis fascia snugly about it. A McVay Bassini type of repair was done, using a strip of full-thickness skin to reinforce the area as well as the internal inguinal ring. He was placed on penicillin and streptomycin postoperatively. His postoperative temperature did not go over 99 F. and he was discharged on his fourth postoperative day. Aside from the usual amount of induration present in the area, he had an uneventful recovery. One year later there is no evidence of recurrence.

Case 4. Mr. F. J., aged 49, had had a right inguinal hernia for 30 years. He sought help because the hernia interfered with his activities. He had had 2 episodes of incarceration and recently noted epigastric distress and increasing constipation.

General physical examination revealed, in addition to a large scrotal hernia, blood pressure of 150/90 and a 2 plus benign prostatic hypertrophy. Laboratory studies were within normal limits.

At operation a large internal ring was encountered. A McVay-Bassini repair was done, using a large full-thickness graft to help close the internal ring and to reinforce the floor of the inguinal canal. A drain was left in the scrotum for 2 days. He was placed on penicillin and streptomycin postoperatively. His temperature went to 100.2 F., then gradually subsided to 98.6 F. by the fourth postoperative day. He had some swelling and ecchymosis of the scrotum and testicle, otherwise his recovery was uneventful. A good result was noted on examination 1 year later.

Case 5. Mr. S. M., aged 47, had a right inguinal hernia 10 months previously in another hospital.

General physical examination was normal except for a right recurrent inguinal hernia. Laboratory findings were within normal limits.

At operation a large, well developed indirect inguinal hernia was identified. After removal of the sac and freeing the cord of excessive fat and tissue, the internal inguinal ring was narrowed. The conjoined tendon then was sutured to Cooper's ligament, following which this area was reinforced by the use of a strip of skin as a suture to approximate the internal oblique to the inguinal ligament. The cord then was placed between the imbricated leaves of the external oblique aponeuroses. He was given penicillin and streptomycin postoperatively and had an uneventful recovery. Examination 1 year later revealed no recurrence.

Case 6. Mr. T. H., aged 44, had had a hernia since the age of 2½ years. During his early life, it was controlled by the use of a truss. At the age of 35 years it was repaired. This repair held well until approximately 8 months prior to his present hospitalization, at which time he noted a recurrence of his hernia.

General physical examination was entirely normal except for a right recurrent inguinal hernia and a mild prostatic hypertrophy of a benign type. Laboratory findings were normal.

Operative exposure of the inguinal canal revealed a direct hernia with the urinary bladder being included in the medial border of the sac. The sac was opened and the contents reduced. The sac, except for that portion containing the urinary bladder, was closed with a running silk suture. The conjoined tendon and transversalis fascia were sutured to Cooper's ligament in the form of a McVay inguinal herniorrhaphy. A strip of full-thickness skin was used to reinforce the area. The cord structures were placed between the 2 leaves of the imbricated external oblique aponeuroses. Postoperatively he was given penicillin and streptomycin. He made an uneventful recovery.

SUMMARY

We have presented a technic for the repair of difficult inguinal and incisional hernias, using full-thickness skin to reinforce the deficient fascia at the hernia site. This skin has been used both as a patch and as a strip woven into the area. The cases of 6 patients on whom this technic was utilized are presented. The results have been good. We have been selective and have used this method only on patients who had difficult hernias. We believe that it has a definite place in the armamentarium of the general surgeon.

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DISCUSSION

I was requested to discuss this paper because Doctor Storey could not be present. Consequently, I have not had the opportunity of studying the details of this report. I do not favor burying skin, either full-thickness or dermal grafts.

Davis and Trout[1] demonstrated the tendency with which sebaceous glands resist degeneration. Quote "—we note that degenerative processes are also going on in the transplant. The epidermis suffers must and in nearly all grafts there is a complete slough of the epithelial layers, distal to the Malpighian layer, and even in this stratum there is always a very considerable thinning of the cells. In the corium, the connective tissue elements undergo marked destruction, including that of the vessels. The endothelium of the vessels degenerates and except in an occasional area become completely necrotic. The hair follicles and sebaceous glands show little degeneration and consequently little repair. They are the most viable elements of the skin and in a successful graft show no alteration whatever. In a sloughing graft, they are the last elements to disappear."

Recently an instance was brought to my attention where, upon reoperation for recurrence of an inguinal hernia, the mass in the inguinal canal proved to be an accumulation of sebaceous debris from proliferation of a buried cutis graft.

It is my impression that all too frequently and without justification, inert materials or free grafts are used to repair tissue defects. It has been my experience that sufficient tissues are available locally to effect adequate repair whether the defect is in the inguinal region or is a ventral hernia.

Should it become necessary to use accessory tissue to bridge a defect, I should favor fascia taken from the patient's own thigh.

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SURGICAL COMPLICATIONS OF DIVERTICULITIS AND DIVERTICULOSIS OF THE SIGMOID COLON

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Diverticulosis of the left colon usually is seen in the age groups past 40 years. It has been estimated by various writers as occurring from 7 to 30 per cent in all people after 40 years of age. Bargen[10] reported an incidence of 5.2 per cent in over 70,000 autopsies. At the Massachusetts General Hospital, one third of the patients having barium enemas showed diverticula, and 8.9 per cent of these had evidence of diverticulitis. The rate progressively increases with age.

Little is known about the etiology of diverticula, but the most probable theory assumes that they form where the terminal branches of the mesenteric arteries pass through the muscularis to divide beneath the mucosa. Constipation, diarrhea, overeating, sedentary habits, and the aging process all seem to contribute to their origin.

Diverticulosis, uncomplicated, rarely gives symptoms. Inspissated feces, roughage in the diet, amebic infestations, bacillary dysentery, ill-advised enemas, and catharsis all tend to cause irritation in these pouches. Beginning as a mild inflammation, diverticulitis may progress to abscess formation, perforation, pericolitis with thickening and narrowing of the intestinal lumen, internal and external fistulas, hemorrhage and/or obstruction.

An individual with pain in the left lower quadrant, associated with tenderness, fever and elevated leukocyte count, with or without a palpable mass, should be examined by a contrast barium enema after a sigmoidoscopic examination.

The treatment of acute diverticulitis usually comprises bedrest, heat, low residue diet, mineral oil, antibiotics and/or sulfathalidine. In the course of a week to 10 days the condition most frequently subsides. Following an acute episode, a routine of low residue diet, and the avoidance of constipation will have a tendency to prevent or reduce the frequency of recurrences. One should not refuse surgery to the individual who continues to have repeated attacks with their associated disability and economic handicaps.[4]

Surgical treatment of the complications of diverticulitis is varied. Cecostomy and right transverse divided colostomy are palliative measures frequently indicated.[7] Cecostomy is being used less and less, because the evacuation of gas and fecal matter is not satisfactory. If the distention in the cecum is very great and the condition of the patient is poor, it probably is the safer procedure. Frequently the cecal wall is so distended and ischemic that rupture can occur with very little manipulation.[5]

Right double-barrelled transverse colostomy is the most satisfactory procedure when the choice is optional. With perforation the left lower quadrant should be drained and supportive measures instigated.

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Except in cases of obstruction and perforation, or severe debility, three stage procedures are being done less and less frequently. After the cecostomy or colostomy has been performed, and the patient has responded properly, the bowel should be prepared for the second stage. After the acute infection has subsided and the colostomy has stabilized, both down grade and up grade irrigations of the isolated bowel segment can be started.[12]

For colonic sterilization we recommend oral administration of neomycin 1 gram every 6 hours and sulfathalidine 1½ gram every 6 hours starting 48 to 72 hours before surgery. The isolated segment also can be prepared by instilling these preparations.

The abdomen is opened through a left rectus or pararectus incision. The liver, spleen, and lymphatic glands are routinely explored for evidences of malignancy. The diseased segment of bowel is removed and an end to end anastomosis is performed.

The third stage is performed 2 to 6 weeks later, at which time the colostomy stoma is closed by an end to end anastomosis.

The three stage operation creates a long drawn out, debilitating and expensive program that should be avoided if possible.

When it can be performed a one stage resection of the colon is the operation of choice. In those patients with partial obstruction the bowel can be decompressed by careful enemas and mild saline cathartics. Antisepsis is obtained by the use of neomycin and sulfathalidine. Poth[11] advocates rapid preparation of the intestine by giving 1 gram of neomycin every 4 hours, beginning 1 hour after administering 2 ounces of castor oil. He also recommends the use of 1.5 grams of sulfathalidine with each gram of neomycin for a more effective control of Shigella organisms. A cleansing tap water or saline enema should be given 12 hours before surgery. The abdomen is opened through a left rectus or pararectus incision and explored. The segment of bowel removed should be well beyond all diseased portions if possible. Obviously, if carcinoma is suspected, a more radical operation is performed. An open end to end anastomosis is done.

The two stage operation is reserved for those patients in whom leakage might occur. A right divided transverse colostomy is performed to divert the fecal stream and lessen tension on the suture line. When sufficient time has elapsed, the colostomy is closed by an end to end anastomosis.

The Mickulitz exteriorizing operation is rarely utilized. It creates a long drawn-out convalescence. In addition it is dangerous due to friability of the bowel wall, infection and shortness of the afferent and efferent loops. If carcinoma is present, this procedure is certainly inadequate. It is used occasionally where volvulous with gangrene is present.

Obstruction of the small bowel is not infrequently seen as a complication of

diverticulitis. This is caused by an extension of the inflammatory infiltration beyond the confines of the colon. Such a complication is an indication for emergency surgical intervention.

Frequently abscesses form secondary to diverticulitis. Bedrest, antibiotics and a careful medical regime may result in resolution. If it perforates into the peritoneal cavity, emergency drainage is indicated. Sometimes such abscesses dissect extraperitoneally and burrow through the skin to cause cutaneous fistulas. When this occurs, the patient should be placed at bedrest, antibiotics are given parenterally along with sulfa drugs and other supportive measures. When the acute inflammation has subsided, either a one stage or two stage resection is indicated.

A patient having urinary frequency, dysuria, fecal matter and gas in the urine, should have a thorough examination of the left colon. When only dysuria and frequency are present, it may mean diverticulitis in juxtoproximity to the bladder. This condition usually can be treated by a one stage procedure in which the resection is performed, the vesicocolic fistula, if present, removed and the bladder closed.

During the past few years, hemorrhage as a complication of diverticulitis has been reported more and more.

It is considered good surgical judgement to perform a primary resection in the group of patients under the age of 45 years with repeated recurrences of diverticulitis. This group is most likely to develop severe complications in their early fifties.

SUMMARY

Either a primary colon resection or a staged procedure is indicated in diverticulitis under the following conditions:

(1) Those not responding to medical treatment.
(2) Recurrences in the younger age groups.
(3) Perforation with peritonitis.
(4) Fistula formation;
    a. Cutaneous fistula
    b. Enteroenteric fistula
    c. Vesicocolic fistula.
(5) Carcinomatous degeneration.
(6) Small bowel obstruction.
(7) Obstruction or severe residual deformity of the sigmoid colon.
(8) Associated urinary symptoms.
(9) Bleeding.

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DISCUSSION

As the average life span of man increases, the problem of diverticulosis and diverticulitis and their complications assumes a role of increasing importance in the practice of every surgeon. Dr. Littlefield, in the time allotted to him, has reviewed admirably the various accepted methods of treatment of these complications, and to this I can add little.

It seems to me however, that we should focus our attention on the prevention of diverticulitis rather than on the treatment of its complications. Today, with more routine annual physical examinations being done, many including barium enema, we have a golden opportunity to wage a war of prevention. All too often internists and surgeons alike have dismissed as incidental roentgenologic diagnosis of diverticulosis particularly so when the concern has been as to whether a malignancy was present. Upon learning that a patient has diverticulosis our objective should be clear—to prevent this individual developing complications secondary to this basic anatomic defect. Just as in cholelithiasis, we do not wait for the stones to occlude the common duct before instituting treatment, in diverticulosis we should not wait for its complications to occur before beginnng therapy aggressively and vigorously.

Assuming as we must, that the change from diverticulosis to diverticulitis is brought about by a fecolith in the diverticula secondary to constipation and straining, we must take every measure available to us to eliminate these predisposing factors. I will not go into the treatment of constipation in detail, but suffice it to say that the patient must be placed on a low residue diet, advised to take fluids in adequate quantities, and given regular daily prophylactic doses of mineral oil or whatever laxative to which he responds the most readily. Even more important than these measures is the absolute necessity for the patient to respond to each urge to defecate rather than postponing this to a time more convenient to him.

Even on this regimen there are those who will develop diverticulitis, but I am firmly convinced that the great majority, if not all, initial attacks can be controlled conservatively if adequate treatment is instituted early. Once the acute

episode has subsided, what should be our course? If we see a patient who has had an attack of acute cholecystitis we don't wait until another attack before doing something definitive, so why should we manage diverticulitis any differently? Procrastination only allows the patient to become older and a poorer operative risk, as well as increasing the chances of complications with a second attack. I am certain that if we adopt a more aggressive approach to this disease and advise early resection after the initial attack of diverticulitis we will but rarely encounter the devastating complications of which Dr. Littlefield has spoken.

If we could all be made to appreciate what a threat these complications are to the life of the individual concerned and what an overwhelming financial burden this is to the man who has retired on a small pension and is too old to obtain employment again, we would not look at the roentgenologic report, "diverticulosis of the sigmoid colon", and send the patient on his way with the assurance that there is nothing wrong with him.

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DISCUSSION

Doctor Littlefield asked me to discuss the question of the relationship of antibacterial agents to surgical treatment of diverticulitis. For this purpose I shall divide diverticulitis into essentially four groups:

1. The abrupt, acute attack.
2. The recurring attacks superimposed upon practically constant lower abdominal pain with possible mass which is not exquisitely tender.
3. The development of an exquisitely tender mass with high grade of lower abdominal tenderness and fever.
4. The development of perforating abscess and fistula.

Every attempt should be made to allow the acute phase of the disease to subside and suppuration to become localized. Frequently gastric suction is instituted. Penicillin and streptomycin are given parenterally. If feasible neomycin and sulfathalidine are given by mouth even though gastric suction will need be interrupted for a period to allow the drugs to pass out of the stomach. A parasympatholytic drug, such as pamine, is given in large doses to reduce the secretion of fluids into the gastroenteric tract. Parenteral fluids are administered. Careful observation usually will show improvement within 12 hours. Continue conservative, supportive treatment so long as condition improves. If extensive suppuration has not occurred, the condition will subside and permit study and definitive treatment in the interval.

Should the disease fail to respond to conservative treatment, a colostomy is performed. *Do not explore the abdomen at this time! Do not be tempted to palpate the lesion!* Involvement of the cecum and ascending colon presents a special and difficult problem. A fistula should have adequate drainage especially if it is complicated by a large abscess.

Ultimately, after the acute phase of the disease has subsided, the bowel is prepared in the usual manner for resection. Neomycin and sulfathalidine are used as the appropriate intestinal antiseptics. Once a segment of bowel containing diverticula has been involved in an inflammatory process, it should be resected. In this respect we must take very much the same attitude as that assumed in the treatment of appendicitis. I must take issue with Doctor McClure, if I correctly understood him to advocate the resection of the colon merely because of the presence of diverticulosis.

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USE OF NEGATIVE PRESSURE AS A METHOD OF DRAINING EXTENSIVE WOUNDS

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The importance of adequate drainage following radical mastectomy is well documented. Chase[1] stated that "adequate post-operative drainage is of paramount importance. Serum collections and clots must be strictly avoided as one of the most common causes of lymphedema of the arm. Three drains are routinely placed." Keyes, Hawk, and Sherwin[4] reported that they frequently use up to 5 Penrose drains. Deaton and Bradshaw[3] found that serum collection postoperatively, with resultant infection, was the single most important etiologic agent in postmastectomy edema of the arm.

As an aid to adequate drainage, Orr[5] reported the use of "tension sutures" to hold the skin down tightly against the intercostal muscles, thus lessening the possibility of serum accumulation. Keys, Hawk and Sherwin[4] subsequently confirmed Orr's report, listing multiple benefits to be incurred through the use of "basting sutures", as they called the sutures used to fasten the skin to the intercostal muscles.

However, in spite of multiple drains and fixation of the skin flaps to the chest wall, serum collections still occurred in some patients. In December 1952, Raffl[6] reported the use of negative pressure drainage following radical mastectomy. He had found that with the use of a Robinson catheter, usually a size 16F, and negative pressure, his breast amputation wounds healed with practically no serum formation, there was a minimum of marginal necrosis, and the patients were infinitely more comfortable with the lighter dressing that could be used, since no compression was needed.

This procedure was adopted and used as a method of postoperative drainage in several mastectomy wounds. All that Raffl had claimed was found to be true. Subsequently, the use of negative pressure drainage has been extended to include many types of wounds, wherein large skin and/or subcutaneous flaps were raised during the procedure. In no case has aspiration been necessary, and it is believed that many flaps have survived that would have sloughed with ordinary drainage. This is attributed to the fact that with negative pressure drainage the flaps are held snugly against the underlying tissue, and capillary permeation into the flap is thereby facilitated.

The types of cases in which postoperative negative suction has been employed include radical neck dissection, axillary dissection, inguinal node dissection and hind quarter amputation, as well as mastectomy.

The technic is quite simple. Usually 2, size 20F catheters are used, one at the superior margin of the wound, the other at the inferior margin. Multiple perforations are made in the tubes so that suction is applied throughout the extent of the buried part of the catheter. It has been found best, when extensive flaps are

FIG. 1: Catheter negative suction drainage following radical neck dissection. Notice how skin is drawn tightly against the underlying structures. Although the skin edges appear blue, there was no necrosis.

FIG. 2: Catheter negative suction drainage following hindquarter amputation. Notice catheters are introduced through skin that has not been undermined.

present, to insert the catheters through that part of the skin not undermined, thus making the seal a little better, and perhaps contributing to the viability of the flap. Of necessity, the wound must be closed air tight, or sealed with vaseline gauze, to prevent leakage. Any source of mild suction may be used, such as the mechanical Burdick-McLellan Unit, as described by Deaton[2], or a simple gravity unit, such as the Wangensteen apparatus. The tubes are removed as soon as drainage ceases, which is usually 48 to 72 hours postoperatively.

SUMMARY

The use of negative suction is described as a method of drainage for extensive wounds.

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USE OF LYOPHILIZED HOMOGRAFTS OF DURA MATER IN THE REPAIR OF INGUINAL HERNIAS*

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In April of 1954 we made a preliminary report[2] before the Southwestern Surgical Congress on the use of lyophilized fascia lata as a suture material for the repair of hernias. During 1953 and 1954, 65 incisional and 27 large inguinal hernias were repaired with the fascia, using a technic[3] similar to Gallie's. The recurrence rate in this series of patients (all of whom were carefully followed), was disappointing. There were *32 per cent* recurrences among the incisional hernias and *14 per cent* among the inguinal hernias.

Our figures closely parallel the recurrences reported by Burdick and Higinbotham[1] in 1937 for a series of 975 hernias repaired with autogenous fascia lata at The Hospital for Ruptured and Crippled in New York City. Their recurrence rate was *29.1 per cent.*

During the period when we were using lyophilized fascial strips to repair hernias, we were also using it to close the abdominal incisions in a series of 22 cancer patients. In 13 of these cancer patients, sections of the wound were obtained at autopsy for histologic examination. We also obtained biopsies from 12 of the recurrent hernias that were reoperated upon making a total of *25* specimens for study. Gross and microscopic examination of these specimens showed that the fascia was still present in all of these patients. It was slowly replaced by white fibrous tissue from the host, and always in the exact pattern of the homograft. There was minimal foreign body reaction. There appeared to be firm bondage between the graft and the host tissue.

The 18 recurrences which we reoperated upon seemed to be due to mechanical factors such as tension, slipping of the fascial strip from transfixing sutures, and the large holes caused by the Gallie needles. The fascial strips were found to be intact with no evidence of dissolution. In all of the 18 patients reoperated upon we were able to identify and dissect out the transplanted fascia.

Because of the persistence of the homologous fascia, its replacement by fibrous tissue of the host, and the fact that it caused so little foreign body reaction, we were encouraged to consider other means of using lyophilized homologous fascia for hernia repair.

Since dura mater is composed of the same white fibrous tissue that is present in fascia lata, we decided to try this membrane as a "patch" graft. Dura mater is an exceedingly tough membrane, consisting of two layers of white fibrous tissue with the collogenous fibers of each layer running at right angles to the other. It is

* From the Department of Surgery of the Baylor University College of Medicine.
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Lyophilized dura mater may be obtained from Taylor Laboratories, Inc., Houston 4, Texas.

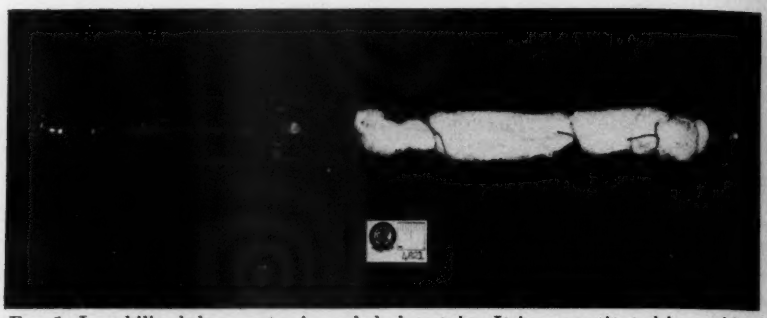

FIG. 1. Lyophilized dura mater in sealed glass tube. It is reconstituted by soaking in saline solution for 10 minutes.

FIG. 2. Fresh dura mater on the left, reconstituted lyophilized dura on the right. Note similarity in appearance. Strip of fascia lata below for comparison.

resistant to tear in any axis and holds sutures well. The dura covering of one hemisphere measures approximately 15 by 10 cm. and is slightly convex (fig 2). We found this size membrane to be well suited to the repair of large inguinal hernias.

TECHNIC

The technic employed was as follows: After the sac of the inguinal hernia has been dissected out and ligated, an incision is made through the transversalis

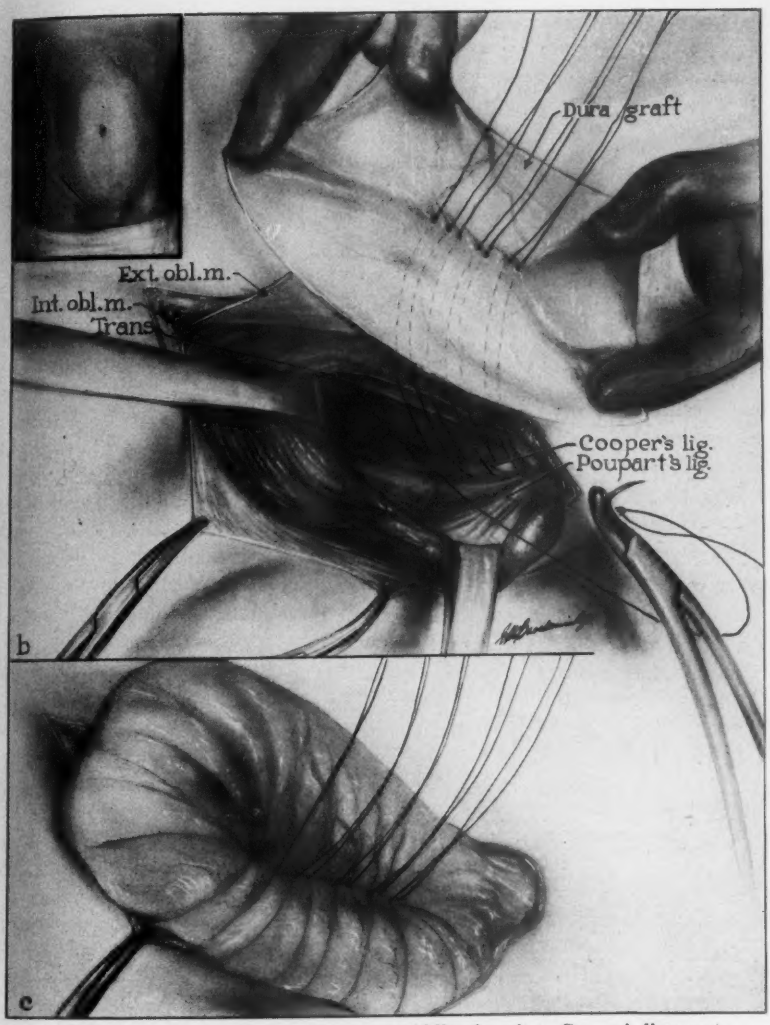

FIG. 3. Technic of repair. Anchorage of middle of graft to Cooper's ligament.

fascia in the floor of the inguinal canal and Cooper's ligament is exposed. Five or 6 interrupted sutures of no. 0 silk are placed through the middle of the homograft and through Cooper's ligament as shown in the illustration (fig. 3). It is best to place all of these sutures before tying them. A Heany needle-holder facilitates the placing of these sutures. The angulated jaw of this instrument allows the needle to be placed through Cooper's ligament without fear of injuring the femoral vessels. These sutures then are tied, giving a deep and firm anchorage to the middle of the graft. The upper edge of the cut transversalis fascia then is sutured to the

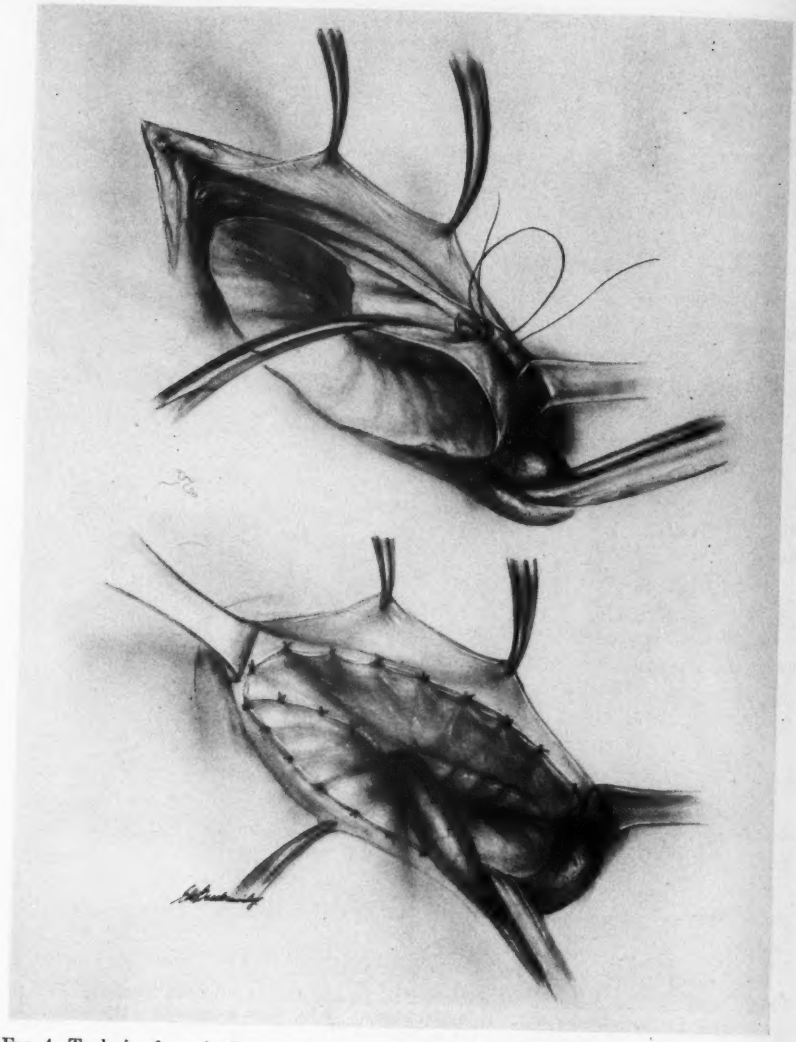

FIG. 4. Technic of repair. Suture of transversalis fascia to graft and the completed repair.

under surface of the upper portion of the homograft from the symphysis pubis to the internal ring (fig. 4). The upper edge of the homograft then is sutured to the conjoined tendon and to the anterior rectus sheath. Laterally, a slit is made in the graft to accommodate the cord and the graft is sutured to the internal oblique muscle lateral to the cord. The lower portion of the homograft is sutured to the shelving edge of Poupart's ligament and medially the graft is sutured to the pubic

tubercle. The external oblique fascia then is closed over the cord without transplanting it.

At the conclusion of this procedure, the graft will be securely anchored to Cooper's ligament and to other surrounding structures in such a manner that a firm new floor for the inguinal canal is created. This homograft will be replaced by fibro-plasia and a permanent layer of white fibrous tissue will be laid down in the exact pattern of the homograft.

RESULTS

Twenty inguinal hernias have been repaired since January 1955 using this technic. Only large direct and large indirect inguinal hernias with a weak floor were included in this series. All of these patients have been followed up and re-examined at 6 month intervals. There were no wound infections or serum collections in any of the patients. There have been no recurrences to date.

While it is too early to evaluate this technic on the basis of recurrences, results so far have been encouraging enough to warrant further trial of the method.

From our experiences with the fascia lata and our histologic studies of the fate of this transplanted tissue, we believe that the dura grafts are replaced by white fibrous tissue from the host and that this sheet of living fascial tissue will conform to the pattern and position of the graft. We have found this to be true in dogs in which we have implanted the dura over muscle and fascia and later observed the wounds at autopsy.

We believe this technic of inguinal hernia repair has the following advantages over more conventional types of repair.

1. Since the dura is sewn to surrounding structures in their normal position, there is no tension and little likelihood of the sutured tissues being pulled apart.

2. The deep anchorage of the graft to Cooper's ligament re-enforces the inguinal floor at its most vulnerable point.

3. The lyophilized dura mater has been found to excite very little foreign body reaction. It serves as a structural framework for the formation of white fibrous tissue by the host which conforms to the pattern of the graft.

4. The abundant supply of dura mater in the autopsy room and the increasing use of freeze-drying for tissue preservation will make it easily available in the near future.

Addendun: Since December 1954, 31 inguinal hernias have been repaired using this technic. All patients have been examined at 6 month intervals and as of December 1956, there have been no recurrences.

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DISCUSSION

Doctor Usher is to be commended on the presentation of a very interesting subject. He also is to be commended for his originality in the use of dura mater as a graft. I feel very inadequate in discussing the paper as I have had no such experience. However, I had a very competent librarian searching the literature for evidence of its previous use and none could be found. I also talked with Doctor Usher just before the meeting and he had been unable to find any reference in literature. Doctor McVey has ably pointed out that a predisposing factor in the formation of incisional hernias in vertical incisions is the stress of the closure being opposed to the longitudinal fibers of the aponeurosis. The strength of the aponeurosis lies in a vertical manner along the course of the fibers and not across the fibers. It would seem that the dura mater with its 2 layers and fibers running in opposite directions would fill this mechanical qualification. This is further brought out by Doctor Usher's finding that with the fascia lata grafts, the host layed down connective tissue fibers in the direction of the fibers of the graft. This also is true in his experimental work with the dura mater. Thus, we can anticipate that we would get maximum strength in all directions and not merely in one direction, so that this should make an ideal type of prosthesis. In addition, there was apparently little adverse reaction by the host to the dura mater.

In my personal experience with other types of re-enforcing materials I find that the most important thing is to get complete cohesion between the various layers and the prosthesis. In large incisional hernias it is necessary to dissect wide areas and inevitably, despite meticulous care, there is considerable oozing of serum. Routine drainage with rubber drains do not adequately drain this wound. The exits will congeal and it will be necessary to probe and release large amounts of serum. This causes the tissues to float away from the grafted material. On a number of patients I have used constant suction through a catheter and it has worked admirably in keeping the wound completely dry and allowing good cohesion of the various layers. Approximately 750 cc. of serum will be collected from the average repair of an incisional hernia. This problem does not exist in inguinal hernias.

Again, I wish to commend Doctor Usher for this stimulating and original work.

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POSTOPERATIVE PSEUDOMEMBRANOUS COLITIS: HEMICOLECTOMY WITH RECOVERY

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Although uncommon, postoperative pseudomembranous enterocolitis may develop with devastating suddenness, and rapidly progress to a fatal termination. If recognized and treated sufficiently early, the almost inevitable dehydration, shock and death may be avoided. Too often, the diagnosis is made at the autopsy table, the mortality rate of the condition being over 70 per cent.

Etiology: The occurrence of the condition has been recognized with increasing frequency during the past 3 decades. The etiology, however, has remained obscure.

A comprehensive paper, based upon the cases of 40 patients who came to necropsy, was published by Penner and Bernheim in 1939.[6] These workers concluded that shock during the operative procedure initiated the process which culminated in a necrotizing enterocolitis. In the cases studied, it appeared that shock was a common pathogenic factor resulting in an intense compensatory vasospasm followed by necrosis and sloughing of the mucosa of the intestinal tract. This etiologic concept has not received wide acceptance nor has it been entirely abandoned.[4]

Within the past 5 years, there has been an increasing awareness of a syndrome presenting an almost identical clinical and pathologic picture but occurring as a complication of antibiotic therapy.[1–3, 5, 8–10] These cases develop as a result of an overgrowth of a resistant strain of Micrococcus pyogenes which produces an enterotoxin that causes similar lesions in the intestinal tract.

This latter concept, however, does not explain the etiology of the cases which occurred prior to the development of the antibiotic agents. In 1954, Pettet and co-workers[7] of the Mayo Clinic analyzed 94 fatal cases occurring over a 27 year period. Roughly half of the cases occurred during the preantibiotic era and half after the antibiotics came into wide range. Based on these findings, it was concluded that there was not an increased incidence since the advent of antibiotics. They also were of the opinion that no one etiologic factor was responsible.

In the series of 94 cases reported by Pettet, 80 per cent of the cases followed operative procedures on the gastrointestinal tract; and in 44 per cent of the cases, the diagnosis was carcinoma of the colon. Although most of the cases occur in postoperative patients, the condition occasionally appears in patients suffering with medical disabilities.

It is reasonable to conclude that there are two important entities: '*idiopathic*' pseudomembranous enterocolitis and Micrococcal enterocolitis.

Pathogenesis: In surgical patients, the onset of the syndrome usually occurs from the third to the eighth postoperative day. The symptoms and clinical findings are fairly uniform consisting of fever, leucocytosis, severe diarrhea,

weakness, lethargy, abdominal pain, tenderness and gaseous distention, rapidly progressing to irreversible shock and death within a day or two unless prompt and vigorous therapy is instituted.

In a postoperative patient, the signs and symptoms often suggest an intra-abdominal emergency, such as hemorrhage, leakage of an anastomosis or bowel obstruction, which leads to reopening the abdomen.

At autopsy, the intestinal tract is found to be markedly dilated, either in part or throughout its entire length. Evidence of peritonitis is present in about half of the patients. When the intestine is opened, large amounts of gas and liquid feces escape; and as much as 5000 cc. of liquid feces within the intestinal tract has been measured at autopsy. The mucosal surface of the bowel is characteristically covered with a yellow-green or tan pseudomembrane varying in extent from small scattered plaques of varying size to a diffuse process extending for a distance of several feet.

The pseudomembrane is composed of necrotic cellular debris, fibrin, a variable number of inflammatory cells and some mucous. There is a severe ulcerative colitis with necrosis of the mucosa and extension of the necrotic process into the deeper layer of the bowel in some areas. The submucosal vessels are widely dilated and engorged and occasionally a very recent thrombus is seen within a dilated submucosal vein.

The case to be reported is of interest since apparently it represents the occurrence of pseudomembranous enterocolitis in a patient who had not received any previous antibiotic medication and in whom the abdominal cavity was not entered at the time of the original operation. The ultimate method of management was also different from what has been previously reported.

CASE REPORT

The patient was a 68 year old woman who had generally been in good health. Six weeks before admission, during an episode of paroxysmal coughing, she had suddenly developed a protrusion through the vagina. The symptoms of a pronounced cystocele and rectocele progressively increased during the ensuing 6 weeks. The patient had had 6 term pregnancies. Uneventful menopause occurred at 48 years of age. An appendectomy and oophorectomy had been performed at 25 years of age.

Physical examination revealed a fairly well preserved elderly woman weighing 146 pounds. Positive findings included a mild hypertension, a right rectus abdominal scar, a marked cystocele, a moderate rectocele and a small uterus with no prolapse.

Routine preoperative laboratory findings were within normal limits.

On May 24, 1954, a dilatation and curettage, amputation of the cervix and an anterior and posterior colporrhaphy were performed without incident. Her blood pressure remained stable during and following the operative procedure.

The postoperative course was uneventful until the third postoperative day, when there was a temperature rise to 102 degrees, the onset of diarrhea with 7 or 8 loose stools, vomiting, abdominal tenderness and gaseous distention in spite of the frequent bowel movements. Leucocyte count at this time was 9,000 per cu. mm. The operative area appeared to be in satisfactory condition and no evidence of hematoma or abscess formation could be detected. Urinalysis revealed many red blood cells, presumably as a result of an indwelling catheter, but no pyuria was noted.

The possibility of the presence of pseudomembranous enterocolitis was considered at this

time. Sufficient parenteral fluids to replace losses were administered, and a penicillin-streptomycin combination was given. Her pulse and blood pressure determinations were made frequently, and blood was available if the patient should develop evidence of shock.

During the next 4 days, the patient's condition remained about the same; or at least, it did not deteriorate rapidly as would be expected with pseudomembranous enterocolitis. Her temperature ranged between 99 and 100 degrees with a pulse rate of 90 to 100. Vomiting decreased as did the diarrhea. However, abdominal tenderness and distention persisted together with pain and lethargy. Routine stool examinations and cultures, ordered earlier, were negative for any pathogens. Roentgenologic examination of the abdomen revealed moderately distended large and small bowel loops.

The foremost diagnostic possibility at this point was an incomplete bowel obstruction, probably due to adhesions from the operative procedure in 1911. The general status of the patient was poor, but it was thought that laparotomy should be done.

One week following the perineorraphy, laparotomy was performed through a right lower quadrant transverse incision. After the abdomen was opened, the small bowel and right colon were deflated with the Barnes aspirator to facilitate exploration. Nothing was found in the pelvis as a result of the cystocele-rectocele repair to account for the patient's symptoms. There were some adhesions in the cecal region, and it originally appeared that the sigmoid colon had been caught in the old operative area with a resulting incomplete volvulus causing the obstructive symptoms. The involved bowel was freed and a colon tube per rectum was passed up into the sigmoid.

Although some adhesions had been found, it could not be definitely believed that they were of sufficient extent to explain the entire clinical picture.

The omentum was elevated to inspect the transverse colon, and then it was noted that there were 3 areas on the posterior surface of the left transverse colon which appeared necrotic. Each area measured approximately 3 centimeters in diameter and had a dull, grayish, ischemic appearance on the serosa. There had been no leakage of bowel content through these areas; but it appeared certain that subsequent perforation with peritonitis would develop unless a resection was done, even though the risk, in this instance, seemed formidable.

It was surmised that enterocolitis was the underlying process, but it was difficult to definitely delineate the involved portion because the whole bowel was thick and edematous due to the long-standing distention. In order to go widely beyond the necrotic areas, it was elected to resect the entire transverse colon, splenic flexure and descending colon. This was

FIG. 1. Proximal end of resected transverse colon showing pseudomembrane extending to the line of resection.

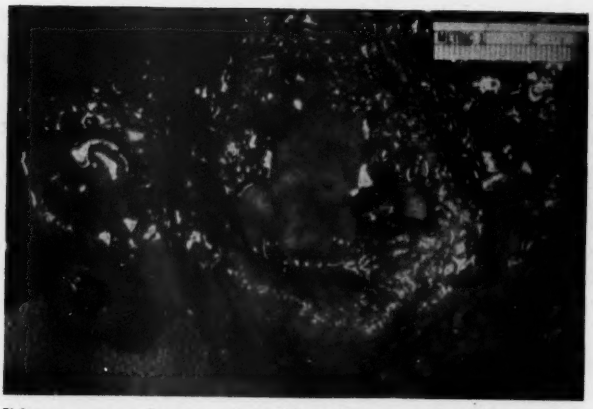

FIG. 2. Midtransverse colon at point of heaviest pseudomembrane overlying area of impending perforation.

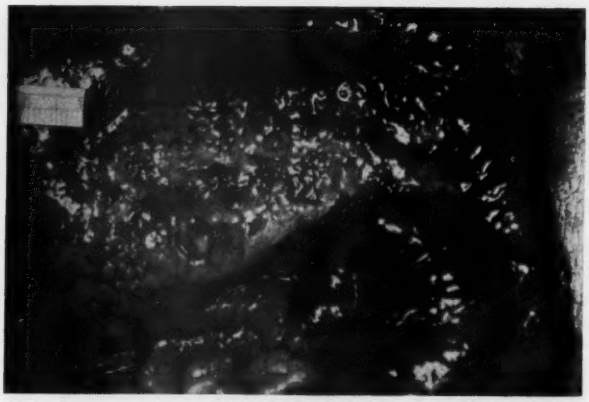

FIG. 3. Splenic flexure region depicting marked edema of mucosa with complete loss of mucosal folds and the distal extension of the pseudomembrane formation.

accomplished, and the remaining portions of the colon were mobilized to allow approximation at the left end of the extended incision as a double barrel colostomy. The procedure was performed as an obstructive resection using the Rankin 3 bladed clamp.

Resection of this length of involved colon seemed rather heroic because it was recognized that the involvement most certainly extended beyond the area of resection; but, at least, the area of impending perforation had been removed.

The gross appearance of the resected bowel is shown in the illustrations (Figs. 1–3). Microscopic sections revealed pseudomembrane formation, a severe ulcerative colitis and early necrosis of the entire bowel in some areas.

Although all cultures were negative for enteric pathogens or Micrococcus pyogenes, the patient was given erythromycin postoperatively as the indicated antibiotic.

The proximal colostomy was opened in 48 hours, and the patient made a slow but steady recovery. Subsequently, the spur was crushed and the colostomy was closed 3 months following the original operation.

COMMENT

No cases have been found reported in the literature in which a resection of bowel has been done for this condition. Although the result in this instance was successful, it should not be implied that this is the indicated treatment in most patients. Although this patient was critically ill, this must have been a relatively mild case of *'idiopathic'* pseudomembranous enterocolitis, because she survived for 5 days with only supportive therapy. The most severe involvement was segmental in the colon. In most of the fatal cases the patients die with severe dehydration and shock due to the profuse loss of fluid through the bowel. At autopsy, varying lengths of the small and large bowel are found to be involved; and the extent of involvement probably is related to the severity of the symptoms.

With only a short segment of bowel affected to a marked degree, the patient did not develop an uncontrollable fluid loss. She probably would have subsequently died of generalized peritonitis had this process not been recognized at the time of laparotomy for a supposed intestinal obstruction.

SUMMARY

A case of *'idiopathic'* pseudomembranous enterocolitis has been presented which occurred following a surgical procedure requiring no invasion of the peritoneal cavity. The patient received no antibiotic preparations prior to the development of symptoms of enterocolitis. No evidence suggesting an infection by Micrococcus pyogenes was found either on culture or microscopic examination of the resected bowel. An extensive resection of involved colon was performed, including areas of impending perforation.

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EXPERIMENTAL ATTEMPTS TO PRODUCE PANCREATIC PSEUDOCYSTS IN THE DOG

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Clinical experience indicates that abdominal trauma is one precursor of pseudocysts of the pancreas. Of 117 patients with pancreatic pseudocysts collected from the literature by Korte,[6] there was a definite history of trauma in 28 per cent. The factor of trauma has been repeatedly discussed in the literature since that time; its incidence preceding pseudocysts ranging from zero in the smaller series to as high as 52 per cent.[8] The more recent literature would place the incidence at no more than 25 per cent. It is evident, however, that in certain patients, pseudocyst formation follows blunt trauma to the pancreas in a cause and effect relationship.

Pancreatitis and biliary tract disease are other factors which have been mentioned in the etiology of the pancreatic pseudocysts.[5, 8] The pathogenesis in these instances is not proved, but surgical observations indicate that whatever the inciting mechanism, necrotic pancreas or collection of pancreatic juice incites an inflammatory response and, if the pancreatic collection becomes trapped within the lesser omental sac, the formation of a pseudocyst results.

Little has been done in experimental animals to demonstrate the pathogenesis of pancreatic pseudocysts. Almost all of the available information rests on clinical impressions; a basis which has proved inadequate for the intelligent management of this difficult clinical problem.

The purpose of this investigation has been to study the response of the pancreas to trauma in an effort to elucidate the factors influencing the development of pseudocysts of the pancreas.

METHODS

The experimental animal was the healthy adult mongrel dog (8–15 kilograms). Although the intrinsic anatomy of the dog's pancreas has many similarities to that of the human, it lies in the mesentery rather than being immobilized in the retroperitoneal area.

Sterile technic and phenobarbital sodium anesthesia were used throughout. On each animal the pancreas was exposed through an upper midline incision. Each animal received 250,000 units of penicillin immediately postoperatively and on the first and second postoperative days if they appeared ill. They were maintained on a routine kennel diet.

The pancreas was traumatized in respective animals in the following ways:

1. Ligation of the pancreatic ducts (7 dogs). Both the major and accessory

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pancreatic ducts were exposed,[9] doubtly ligated and divided. In order to achieve exposure, it was occasionally necessary to divide several of the branches of the pancreatico-duodenal artery supplying the duodenum. In order to provide a secretory stimulus in 2 dogs in this group, an intravenous infusion of 100 clinical units of secretin was given for 4 hours prior to ligation of the ducts.

2. Incision of the pancreatic ducts (5 dogs). Injury to the pancreatic duct was planned so that pancreatic juice might escape into the peripancreatic tissues. The main duct was incised longitudinally near its stoma for approximately 1 cm.; the smaller duct was transected. Both ducts were left open.

3. Crushing the pancreas (7 dogs). Using a large hemostat as a crushing agent, the complete cross section of each limb of the gland was crushed near its middle over a longitudinal distance of 2.5 cm. This provided in each limb of the pancreas an area of approximately 2.5 square cm. of crushed pancreas with at least an equal area of uncrushed tissue proximal and distal to the area of injury. In each experiment a hematoma formed at the site of the injury. Bleeding was slight and was easily controlled by compression.

In 2 experiments, the two ducts were ligated and divided immediately before the gland was crushed.

4. Injection of blood into the pancreas (4 dogs). In an effort to produce a pure hematoma of the pancreas, blood was injected into the pancreas of 4 dogs (20–30 cc. each).

5. Injection of pancreatic juice into the pancreas (5 dogs). Having collected fresh pancreatic juice by creating pancreatic fistulas in other dogs, 8 cc. of juice was injected into the head of the pancreas of each of 5 dogs. In most of the dogs, blood extravasated into the pancreas at the site of the injected fluid, requiring a ligature to control bleeding. In several instances, part of the pancreatic juice exuded from the puncture wound into the peritoneal cavity.

6. Injection of a mixture of bile and pancreatic juice into the pancreas (5 dogs). To obtain an activated pancreatic preparation, 4 cc. of autogenous gallbladder bile was mixed with 4 cc. of fresh pancreatic juice. This was injected into the head of the pancreas.

7. Injection of a sclerosing agent into the major pancreatic duct (5 dogs). In an effort to produce gradual obliteration of the pancreatic duct, 1 cc. of 5 per cent sodium morrhuate with benzyl alcohol 2 per cent was injected under minimal syringe pressure into the major pancreatic duct.

RESULTS

An autopsy examination was made on all dogs at the end of 4–6 weeks, except 2 which died on the twenty-third day. At autopsy, special attention was given to the condition of the pancreas, including the presence of adhesions, fat necrosis, or collections of fluid. The results are summarized in table I.

1. Division and ligation of the ducts. In all 7 the dogs the pancreas retained its normal configuration. It was indurated and markedly reduced in size, demonstrating a scar at the site of ligation. All the dogs showed marked weight loss, up to 25 per cent of body weight. One dog died on the twenty-ninth day apparently

TABLE I

Type of Injury	Number of Dogs	Autopsy Finding
1. Division and ligation of ducts.	7	Scar at site of ligation; gland reduced in size and indurated; weight loss of animal.
2. Incision of pancreatic ducts.	5	Ducts sealed by dense scars and omental adhesions; moderate induration of pancreas.
3. Crushing of pancreas.	7	Scar at site of injury; omental adhesions.
4. Injection of blood.	4	Pancreas appeared normal.
5. Injection of pancreatic juice.	5	Dense scar at injection site; omental adhesions.
6. Injection of bile and pancreatic juice.	5	Scar at injection site; omental adhesions.
7. Injection of sclerosing agent into duct.	5	Pancreas indurated.

from malnutrition. He demonstrated a striking weight loss with an absence of peritoneal fat.

2. Incision of the pancreatic ducts. In 4 of the 5 dogs there were firm omental adhesions sealing off the ducts. The pancreas was moderately indurated. One of these died on the thirty-first day of peritonitis secondary to obstruction and rupture of the transverse colon. The fifth dog died of intestinal obstruction on the thirty-sixth day and had diffuse fat necrosis. The main pancreatic duct was open.

3. Crushing the pancreas. All 7 dogs had a narrow constricting scar and omental adhesions at the sites of the crush injury. The pancreas was moderately indurated. No retention cyst or pseudocyst was noted.

4. Injection of blood. At the end of 1 month, autopsy revealed a pancreas which grossly appeared completely normal.

5. Injection of pancreatic juice into the pancreas. All of the dogs had scars and omental adhesions at the injection site. One of the dogs had a marked weight loss; dying on the twenty-third day.

6. Injection of bile. The pancreas revealed only scars and omental adhesions at the injection site.

7. Injection of a sclerosing agent. The pancreas was indurated in each of the 5 dogs. Three had firm white nodules scattered over the surface of the gland which grossly appeared to be pancreatic calcification. Three of the glands were pink, suggesting an increased vascularity.

DISCUSSION

Very little information is available in the literature on the experimental production of pancreatic cysts. As early as 1886, Senn[14] reported a series of experimental injuries to the pancreas of animals. Sectioning, followed by immediate suture, crushing, and laceration of the pancreas were all found to produce a cicatrix at the site of the trauma. In one cat he tied two rubber ligatures ½ inch

apart around the splenic limb of the gland. On the sixth day the animal died and at autopsy a small cyst or collection containing about 12 cc. of clear fluid was found corresponding to the site of ligation. The ligatures had cut through the organ and duct. He concluded that the cyst was a collection of pancreatic juice which had escaped from the divided duct and around which a connective tissue wall had formed.

Berard and Colin[1] removed a part of the pancreas of a pig. The animal died a few weeks after operation from accidental causes and they found a cyst replacing the portion of the gland which had been removed. The cyst was described as being the size of a hen's egg, having no connection with the duodenum, and filled with a clear fluid which was coagulated by alcohol, suggesting to them that the fluid was pancreatic juice.

Thiroloix[15] tied the accessory duct in a dog and injected into the duct of Wirsung 7 cc. of a mixture of soot and carbolized liquid vaseline. The right limb of the gland was resected. Two months later, the pancreas was found to be black and hard, and a portion of sclerosed and normal gland was removed. After another 3 weeks, the dog was killed and a large cystic cavity filled with fluid and calculi was found in the splenic portion of the gland.

By crushing the pancreas of a dog and injecting the resulting hematoma with iodine, Lazarus[7] succeeded in producing a cyst of the pancreas containing 100 cc. of milky fluid.

A sterile 2 per cent solution of calcium chloride was injected into the canal of Wirsung in 3 dogs by Brocq and Binet.[2] Two of the dogs, in which 3 cc. had been used, developed hemorrhagic pancreatitis with fat necrosis. The third dog received 7 cc. of the solution. When the animal was killed on the third day, a pancreatic hematoma the size of a fist, disseminated fat necrosis, and a "*cyst*" in the body of the pancreas the size of a walnut, were found.

Pettinari[10] produced single and multiple cystic spaces following duct ligation and intra-parenchymous injections of alcohol and bile. He was also successful in producing a cyst in at least one instance in which the pancreas was contused.

Estrade[3] described pseudocysts in 4 of 14 dogs in which he had crushed the pancreas. The crushing injuries were produced by means of pliers with and without rubber protectors and by energetic pressure with the fingers. In one animal, a cyst of the head of the pancreas was described as being the size of a chestnut and having gray necrotic walls. In a group of 4 dogs, in which an autopsy examination was made on the fifth to the ninth day, 3 had only cicatrization at the incision. In one it was found that the duct had been sectioned and this dog had pancreatic necrosis and bloody intraperitoneal fluid. Section of the duct of Wirsung was followed by hemorrhagic pancreatitis in 5 of 8 dogs.

In a more physiologic approach to the study of pancreatic trauma, Popper noted the effect of pre- and postoperative feeding on the outcome of sectioning the pancreatic duct. In one series of experiments he transected the main pancreatic duct (27 dogs) and in another series (23 dogs) slit it longitudinally for 1 inch.[11] He found that the dogs which had been starved had less fat necrosis and that the omentum had more effectively sealed the open duct, than in the dogs

which had been fed either pre- or postoperatively. In a few of the dogs in which an autopsy examination was made between the second and sixth day, fluid was found between the omentum and the pancreas. No pseudocysts were described. In another study of experimental trauma to the pancreas, Popper[12] crushed the gland over an area of 1–2 square inches in its central part in 7 dogs. After 2–4 weeks the pancreas was found to be cirrhotic in the crushed portion. None of the dogs had fat necrosis. In another 7 dogs he made a complete transverse tear of the pancreas. When an autopsy examination was made on the animals at the end of 1–3 weeks, only 2 dogs had fat necrosis. All the dogs had a constricting scar at the site of the tear and omental adhesions. There appeared to be no difference between the groups which had been starved and those which had been fed pre- and postoperatively. Popper postulated that severe injuries to the pancreas in the dog produce a secretory inhibition. No pancreatic cysts resulted.

In further investigations in experimental trauma, Popper[13] tore the pancreas of 44 dogs and crushed that of 2. The dogs were divided into groups on which additional modifying procedures were carried out, including leaving fresh blood in the abdominal cavity, placing sterile bile in the abdominal cavity, stimulating pancreatic secretion with alcohol and secretin, devitalizing a segment of omentum, and isolating and depriving of its blood supply a portion of the pancreas. In a few of the dogs killed on the third to tenth day, the region of the tear contained a small amount of walled-off cloudy hemorrhagic fluid. There was little difference between the dogs having bile or blood in the peritoneal cavity and those in which pancreatic secretion was stimulated. The inflammatory reaction around devitalized tissue was more marked when the pancreas had also been traumatized.

According to Gordon-Taylor,[4] the clinical development of pseudocysts may require no more than 10–14 days after trauma, so 6 weeks might be a reasonable period of observation. The rather uniform result of injury to the pancreas in this study has been only the production of a scar. The fact that cystic formation did not occur may perhaps be explained as being due to a secretory inhibition following the injury, evidence for which has been presented by Popper. Perhaps the cystic collections of fluid that have been described by others after short periods of observation have been absorbed by the end of 6 weeks. It would be of interest to see if lesser degrees of trauma would produce more success in forming cysts. The work of Estrade suggests that it might. It had been hoped that injection of a sclerosing agent into the duct of Wirsung might produce a gradual obliteration of the duct with the developing of a retention type cyst, but this did not occur.

SUMMARY

Various traumatic procedures, including division and ligation of the ducts, incision of the ducts, injection of blood, injection of bile and pancreatic juice, and injection of a sclerosing agent into the major duct of the pancreas, which have been carried out in a total of 38 dogs, have been described. In almost every instance the site of the injury was replaced by a scar. In no animal was a pancreatic pseudocyst produced.

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CONTROLLABLE TUBE SPLINT FOR CHOLEDOCHODUODENAL ANASTOMOSIS IN CONGENITAL EXTRAHEPATIC BILIARY ATRESIA

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All too often the problem of progressive obstructive jaundice in the weeks or months after birth is hopeless because of complete atresia of the biliary ducts. Fortunate, however, is the infant with extrahepatic biliary atresia or inspissation of the bile within the ductal system, for restoration of biliary-intestinal continuity can be effected. Surgical exploration offers the only hope for those infants with mechanical obstructive jaundice who do not respond to cholagogues.

Before attempting to dissect out the hilar structures of the liver, the gallbladder should be located and its patency established. If the gallbladder contains bile, there is certainly a patent extrahepatic ductal system. A cholangiogram can be satisfactorily performed through the gallbladder to locate the distal end of the atresia and to distend the ductal structures. Frequently, inspissated material is flushed out into the duodenum and a mechanical biliary obstruction is completely relieved without further surgery. Bile or dye then will be recovered by aspiration from the nasogastric tube which is advanced into the duodenum.

To find only a mucous-filled gallbladder or complete atresia of the gallbladder will necessitate further ductal dissection. Adequate exposure, good lighting and meticulous care will avoid a vascular accident in this area. Needle aspiration of suspicious structures will be helpful. When no extrahepatic duct is found in the hilar region, the liver is probed with the aspirating needle to determine if there are any patent or enlarged intrahepatic biliary radicals. If none are found, the surgeon has little to offer.

In the more favorable case of atresia, biliary-intestinal continuity can be satisfactorily established by anastomosing the common duct, hepatic duct or gallbladder to the duodenum, jejunum or stomach. The procedure of choice is anastomosis of the duct to the duodenum whenever possible. Gross[2] has emphasized the importance of securing an adequate anastomotic lumen by suturing the duct to bowel over a short length of no. 8 or no. 10 rubber catheter. On one occasion he was able to thread the catheter through the gallbladder and proximal common duct so that the catheter could be withdrawn electively after making the anastomosis.[1] In another instance, one of the foreign body rubber lengths failed to expel itself and it perforated the infant's bowel. Short lengths of tubing generally are expelled in time without difficulty.

The desirability of controlling the anastomotic rubber tube splint has led to the idea of using the tip of the nasogastric catheter, which is routinely placed in the stomach. This tube can easily be passed from the stomach into duodenum and incorporated in the choledochoduodenal anastomosis. Several small holes are

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FIG. 2. Naso-gastric tube splint with posterior row of silk sutures of choledochoduodenal anastomosis in place.

FIG. 1. Cholangiogram by anesthetist via naso-gastric tube showing the gallbladder and hepatic ducts (dog).

made on the intragastric portion for gastric suction in the immediate postoperative period. The catheter may be pulled up into the stomach and out of the anastomosis at the will of the surgeon. This procedure has been successfully performed on dogs and would appear to be worthy of clinical trial.

The right subhepatic space is routinely drained. A period of prolonged ileus in the postoperative period is characteristic and intestinal decompression is highly desirable, either with interrupted passage of a nasogastric catheter or else by the establishment of a temporary gastrostomy.

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BILATERAL ADRENALECTOMY FOR ADVANCED CARCINOMA OF THE BREAST

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In 1896, Beatson[1] first removed the ovaries for carcinoma of the breast and noted improvement in 2 of 3 patients. By 1905, Lett[12] had collected 99 cases of patients who had had their ovaries removed. There were marked improvement in 23 patients, and less distinct, although definite changes in 13 more.

Nevertheless, oophorectomy was replaced by x-ray castration and it has only been in recent years that surgical removal of the ovaries has again been utilized in the treatment of this disease.

During the last 5 years, there has been tremendous interest in the palliation of advanced breast cancer based on the concept of hormonal dependence. It has been shown that alterations in endocrine balance can produce effective palliation in many patients. In 1950, Wooley and his associates[20] demonstrated that the adrenal glands produced estrogens and androgens in mice. Then it was observed that women who had had oophorectomy for breast cancer often continued to excrete significant and even large amounts of estrogenic compounds in the urine. Presumably, these were manufactured in the adrenals. From this evidence, it was deduced that both the adrenal cortex and the ovary are capable of secreting hormones that can sustain the growth of breast cancer.

To Huggins,[9] in 1951, belongs the credit for the application of bilateral adrenalectomy and oophorectomy to advanced carcinoma of the breast. With the availability of adequate quantities of cortisone, this procedure could now be carried out safely. The next year, 1952, Huggins and his co-workers[10] in Chicago, and Pearson, West, and associates[19] in New York published reports of the results of bilateral adrenalectomy and oophorectomy in the treatment of advanced carcinoma of the breast. The early reports showed that removal of the adrenal glands was effective in producing regression of mammary carcinoma in about 40 per cent of the patients, but the number of cases reported was too small for adequate evaluation.

During the past 5 years, a number of authors have published reports on the results of bilateral adrenalectomy for advanced carcinoma of the breast. Although four series[3, 7, 11, 14] include 50 to 100 cases, the remainder are comparatively small (3 to 36 cases). When totaled however, they add up to a considerable number. We herewith report 10 cases (table I a, b & c). We have included these in the 379 cases we have found in literature, making a total of 389 (table II) which we have used for analysis.

The technic of the operation[7, 10] and the pre and postoperative care have been adequately described in previous articles.[7, 8]

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TABLE Ia

Bilateral Adrenalectomy for Advanced Breast Cancer
Ten Personally Observed Cases

Patient	Age	Symptoms before Radical Mastectomy	Date of Radical Mastectomy	Pathology Report
C. G.	49	Pain in breast, several weeks	February 1952	Adenocarcinoma, no nodes
E. H.	59	Mass in breast for nine months	January 1948	Scirrhous adenoca, no nodes involved
F. N.	51	Mass, 5 months	February 1952	Mucoid adenoca, no nodes
L. K.	57	Unavailable	1952	Unavailable
D. F.	53	Lump in breast, 9 months; lump in axilla 2 months	October 1954	Scirrhous carcinoma of breast with nodes
C. N.	33	3 cm. mass, 5 months, node palpable in axilla	August 1950	Scirrhous carcinoma with one node involved
E. S.	61	Large mass, 10 by 11 by 6 cm. for 3 months	December 1954	Medullary carcinoma with nodes involved
B. S.	58	Mass 2½ cm. for 6 months	August 1954	Scirrhous carcinoma with nodes
T. Z.	29	Lump in breast and axilla, 3 weeks	November 1953	Medullary adenocarcinoma with nodal involvment
L. G.	58	Two lumps in breast, 4 to 5 weeks	May 1955	Colloid carcinoma no nodes involved

RESULTS: SUMMARIZING TABLE I:

1. All of the 10 patients had very severe bone pain due to metastases. Six were confined to bed as a result of pain. One patient had, in addition to pain, an inflammatory carcinoma of the opposite breast. One patient had a pleural effusion in addition to bone pain.

2. One of the 10 patients (10 per cent) died within 30 days of operation and is considered a postoperative death.

3. Following adrenalectomy, 9 patients had relief of bone pain usually starting 1 or 2 days postoperatively. One patient did not obtain any relief. Five of the 6 bedridden patients could ambulate following the operation. One patient with a pleural effusion showed regression of the effusion. One patient with inflammatory carcinoma of the opposite breast had regression of the inflammatory lesion.

4. The period of relief lasted 5 weeks or less in 4 of the 9 patients who obtained relief. Of the remaining five patients, 4 patients obtained relief for 6 months and 1 patient obtained relief for 11 months.

5. The microscopic appearance of the original breast tumor was evaluated and no correlation could be drawn between the response and type of tumor present.

TABLE Ib

Patient	Duration Between Mastectomy and Occurrence of Symptoms Due to Metastases	Months Between Mastectomy and Adrenalectomy	Date of Adrenalectomy	Date of Oophorectomy	Date Died	Died Months Post-adrenalectomy
C. G.	a) 10–11 mon. (mild pains in neck and scapula area) b) 20 mon. (severe pains confining patient to bed)	21	11/27/53	Oct. 1953	8/54	9
E. H.	a) 5½ yr. later (pains in low back & right hip) b) 6¼ yr later (severe pain confining patient to bed)	75	4/26/54	not done	9/2/54	4
F. N.	a) 2 yr. later (pain noted in shoulder; opposite breast became swollen, indurated & inflamed) b) 25 mon. (severe pain shoulder, neck and arm)	26	4/27/54	not done	10/18/54	5½
L. K.	1 yr. (severe aching pains in rt. heel, knee, left leg, left arm & jaw confining patient to bed)	?	7/6/54	not done	12/23/54	5½
D. F.	a) 3 mon. (pain in left leg, left hip & sacroiliac) b) 6–8 mon. (severe pain confining patient to bed)	10	8/4/55	8/4/55	3/9/56	7
C. N.	4½ yrs. later (severe pain in neck)	60	9/6/55	8/25/55	1/28/56	4½
E. S.	7 mon. P.O. (severe swelling of arm; pain in arm & inability to use arm)	10	9/22/55	9/22/55	12/4/55	2½
B. S.	a) 1 yr. (mild aches and pains chest, shoulders, pelvis) b) one yr. (postmastectomy; severe pain in back confining patient to bed)	13	9/27/55	9/27/55	still living at 11 mon. P.O.	
T. Z.	2 yr. later (severe pain in neck & low back confining patient to bed)	25	12/21/55	Jan. 1954	1/27/56	1
L. G.	a) 6 mon. later (mild pain in back) b) 9 mon. later (severe pain in hip confining patient to bed)	9	2/15/56	2/15/56	still living at 6 mon. P.O.	

TABLE Ic

Patient	Sedation Prior to Adrenalectomy	Sedation Post-Adrenalectomy	Duration of Relief Before Symptoms Were Severe Enough to Require Pre Op Sedation	Subjective Response	Objective Response
C. G.	Demerol 75–100 mg. 2–3 hr. or MS gr ¼ q 3 h	Dilaudid gr 1/20 q 8–12 hrs.	4–5 months	pain relief, ambulation	Pleural effusion disappeared, replacement of bone
E. H.	Demerol 75 mg. q 3–4 hr.	Codeine gr SS Aspirin gr X	2 weeks	pain relief	none
F. N.	MS gr ⅙ q few hr.	Codeine gr SS q 8 hr. Aspirin Gr X	5 weeks	pain relief	Regression of inflammatory carcinoma of other breast
L. K.	Demerol 75 mg. q few hours	Codeine gr SS Aspirin gr X	4 months	pain relief, ambulation	none
D. F.	MS gr ⅙ q few hrs.	Dromoran 6 mg. daily MS gr ⅙ q h s	4 months	pain relief, ambulation	none
C. N.	Demerol 75 mg. q 3–4 hours	75 mg. Demerol q 4–6 hrs.	3 weeks	pain relief	none
E. S.	Demerol 100 mg. 1–2 × per day Codeine 2 gr q 3–4 hrs.	75 mg. Demerol 1–2 × day	1 week	pain relief	none
B. S.	MS gr ⅙ 2–3 × per day Codeine gr ¼	no medication	11 months	pain relief, ambulation	none
T. Z.	Demerol 125 mg. & thorazine 25 mg. q 8 hrs. Demerol 100 mg. q 3 hrs.	Dilaudid gr 1/24 q 3 hr	none	none	none
L. G.	Dromoran 2–5 mg. q 4 hrs.	Dromoran 1 mg. q 6–8 hrs.	6 months	pain relief, ambulation	none

6. Eight of the 10 patients died from 1 to 9 months following adrenalectomy. Two survive now, 11 months and 6 months postadrenalectomy.*

It would appear from the above that in patients with metastases adrenaleectomy results in amelioration of pain. Our best results were obtained with patients with bone metastases.

Analysis of cases in the literature:

Of the 389 cases so far reported, 23 at the time of the reports were too early for evaluation, leaving 366 cases for consideration (table II).

* Of the two surviving patients mentioned the 11 month postadrenalectomy patient expired 12-1-56, 14 months after the adrenalectomy; cause of death unknown, and the 6 month postadrenalectomy patient is still alive and free of pain 12 months after surgery.

TABLE II

Adrenalectomy for advanced carcinoma of the breast
Review of Literature

Author	Total Cases	Too Early for Evaluation	Death Within 30 Days of OR	No Effect	Improvement
1. Cade[3]	56	7	8	12	29
2. Strode[16] Burgess	9	—	—	4	5
3. Pyrah[15] Smiddy	22	7	1	8	6
4. Huggins[11] Dao	100	—	5	56	39
5. Wehrly[18] Perlman	4	—	1	1	2
6. Pearson[14] Lipsett	63	—	—	30	33
7. Bowers[2]	11	—	—	5	6
8. Eddy[5]	7	—	—	2	5
9. Galante[7] McCorckle	50	5	6	19	20
10. Taylor[17]	18	—	2	9	7
11. Parsonnet[13]	3	—	—	1	2
12. DeLarue[4]	36	4	5	8	19
13. Katz Saltzstein	10	—	1	4	5
Totals.....	389	23	29	159	178

GENERAL INDICATIONS

A. Huggins originally thought that there was a correlation between the histologic type of the tumor and the response to adrenalectomy. The subsequent investigators have not found this to be so, although there is still some difference of opinion.

B. There is general agreement in all of the series that the following benefits are obtained.

1. Patients with bone lesions and local recurrences or accessible soft tissue recurrences respond better than those with visceral metastases.

2. Postmenopausal women have a slightly better response than premenopausal women.

3. Premenopausal women who show a response to oophorectomy frequently respond to adrenalectomy, whereas those who fail to respond to oophorectomy do not usually improve following an adrenalectomy.

4. Postmenopausal women should be treated by combined oophorectomy and adrenalectomy since the ovaries continue to secrete estrogens in the postmenopausal state.

C. As yet, no good method of selection of patients who will respond to adre-

nalectomy has been found. Recently, a provocative test for response to adrenalectomy has been suggested,[6] but it has not been used on a sufficient number of patients for clear evaluation.

Results may be divided into three groups:

1. Death within 30 days of operation. Twenty-nine of the 366 patients (7.9 per cent) died within 30 days following adrenalectomy and are considered post-operative deaths.

2. No effect from adrenalectomy. One hundred and fifty-nine of the 366 patients (43.4 per cent) failed to respond to adrenalectomy.

3. Improvement-moderate to marked. One hundred and seventy-eight of 366 patients (48.7 per cent) showed moderate to marked improvement.

Of those who respond to adrenalectomy the average period of remission is 9 to 10 months, although 10–15 per cent of patients will have a remission for at least 2 years.

Improvement was measured by some authors in terms of objective improvement only, while others considered both subjective as well as objective improvement. Subjective improvement is often remarkable. Bone pain shows a dramatic disappearance which usually starts as early as 24 hours after operation. This may allow a bedridden patient to become ambulatory while the objective signs remain. Disappearance of respiratory symptoms such as cessation of persistent cough and hemoptysis from lung metastases has occurred without change in the roentgenologic picture.

Objective improvement can be measured by: (1) reduction in size of tumor mass. (2) healing of skin ulcerations. (3) roentgenologic evidence of recalcification of an osteolytic lesion. (4) disappearance of pleural effusion. (5) disappearance of abdominal ascites.

When patients did respond to adrenalectomy, the changes often were dramatic and astonishing. Bedridden patients were able to ambulate and many with very severe bone pain became entirely free of pain, requiring no sedation, whereas prior to operation, they were taking narcotics every few hours.

SUMMARY

Ten cases of bilateral adrenalectomy for advanced breast cancer are reported.

Three hundred and eighty-nine cases of bilateral adrenalectomy have been collected from various sources in the literature and 10 of our own have been included. Twenty-three cases were too early for evaluation leaving 366 cases for consideration. There were 29 post-operative deaths, 7.9 per cent. There were 159 of 366 patients (43.4 per cent) who were unaffected by adrenalectomy. There were 178 of 366 patients (43.7 per cent) who showed moderate to marked improvement.

Patients who did respond often had dramatic and astonishing relief.

The average period of remission in those patients who respond to adrenalectomy is 9 to 10 months.

Ten to 15 per cent of the reported patients had a remission of 2 years or longer.

Adrenalectomy is a worthwhile procedure for patients with severe symptoms from advanced carcinoma of the breast.

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